

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS)	
CORPORATION,)	
)	
Plaintiff)	
)	C.A. No. 23-975 (RGA) (SRF)
v.)	
)	REDACTED - PUBLIC VERSION
LIQUIDIA TECHNOLOGIES, INC.,)	Original filing date: August 29, 2024
)	Redacted filing date: September 5, 2024
Defendant.)	

APPENDIX IN SUPPORT OF JOINT CLAIM CONSTRUCTION BRIEF

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August 29, 2024

TABLE OF EXHIBITS

Ex.	Description
1	Liquidia's Initial Invalidity Contentions (excerpt)
2	<i>United Therapeutics Corp., v. Liquidia Tech., Inc.</i> , C.A. No. 20-755-RGA-JLH, D.I. 405 (D. Del. Mar. 31, 2022) ('793 Trial Tr., Day 4) (excerpt)
3	2009 Tyvaso [®] Label
4	2004 Remodulin [®] Label
5	Liquidia's June 20, 2022, Corporate Overview (excerpt)
6	Liquidia's 2018 Form 10-K (excerpt)
7	Liquidia's 2019 Form 10-K (excerpt)
8	Proposed Yutrepia [™] Label (2024)
9	Preliminary Injunction Hearing Transcript (April 23, 2024) (excerpt)
10	R. Barst, et al., Clinical perspectives with long-term pulsed inhaled nitric oxide for the treatment of pulmonary arterial hypertension, <i>Pulmonary Circulation</i> 2:139 (2012)
11	C. Lee et al., Practical considerations in the management of inhaled prostacyclin therapy for pulmonary hypertension associated with interstitial lung disease (WHO group 3), <i>Respiratory Med.</i> 196 (2022)
12	U.S. Patent Application Publication No. US 2008/0200449 A1 (LIQ_PH-ILD_00101769)
13	U.S. Patent No. 9,358,240 (LIQ_PH-ILD_00101827)
14	U.S. Patent No. 9,339,507 (LIQ_PH-ILD_00101803)
15	U.S. Patent No. 10,376,525 (LIQ_PH-ILD_00101719)
16	U.S. Patent No. 10,716,793 (UTC_PH-ILD_009772)
17	Definition of "Pulse", Merriam-Webster Dictionary (October 23, 2019), available at https://web.archive.org/web/20191023091508/https://www.merriam-webster.com/dictionary/pulse (LIQ_PH-ILD_00102183)
18	Tyvaso Inhalation System, Instructions for Use Manual (LIQ_PH-ILD_00002547)
19	Transcript from the March 10, 2024 Deposition of Steven D. Nathan, M.D. (LIQ_PH-ILD_00000677)
20	International Publication No. WO 2017/192993 A1 (LIQ_PH-ILD_00102194)
21	International Publication No. WO 2019/237028 A1 (LIQ_PH-ILD_00102338)
22	Liquidia's First Amended Invalidity Contentions (excerpt)
23	Transcript from the April 6, 2024 Deposition of Richard Channick, M.D.
24	Letter from Liquidia to UTC (Aug. 2, 2024)
25	U.S. Patent No. 10,786,482
26	OPTINEB [®] -ir Operating Instructions (LIQ_PH-ILD_00002406)
27	VENTA-NEB-ir A-I-C-I Operating Instructions (LIQ_PH-ILD_00002935)

EXHIBIT 1

REDACTED - PUBLIC VERSION

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS
CORPORATION,

Plaintiff,

v.

LIQUIDIA TECHNOLOGIES, INC.,

Defendant.

C.A. No. 1:23-cv-00975-RGA

HIGHLY CONFIDENTIAL

**DEFENDANT LIQUIDIA TECHNOLOGIES, INC.'S
INITIAL INVALIDITY CONTENTIONS**

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study, the authors still found that “daily treatment with sildenafil in patients with [IPF] and known pulmonary vascular disease have suggested improved exercise tolerance, reduced degree of dyspnea, and improved quality of life.” (Zisman D, et al., A Controlled Trial of Sildenafil in Advanced Idiopathic Pulmonary Fibrosis, *New Eng. J. Med.* 363:620-628 (2010) (UTC_PH-ILD_010830) at UTC_PH-ILD_010831.) Dr. Nathan agreed with the authors that the improvements in the secondary endpoints were “statistically significant” and he acknowledged that there was a significant 6MWD improvement in a subgroup of patients with right ventricular systolic dysfunction. (PFF Summit 2019 at 6:54, 7:27.) In the Sildenafil with Pirfenidone study, there were improvements in the UCSD shortness of breath questionnaire and FVC. (Behr J, et al., Efficacy and Safety of Sildenafil Added to Pirfenidone in Patients with Advanced Idiopathic Pulmonary Fibrosis and Risk of Pulmonary Hypertension: A Double-Blind, Randomised, Placebo-Controlled, Phase 2b Trial, *Lancet Respiratory Med.* 9 (2020) (UTC_PH-ILD_009853) at UTC_PH-ILD_009860-61.) In the Iloprost (ACTIVE) study, the authors concluded that “[a]lthough evidence for clinical benefit of prostacyclin inhalation therapy in IPF and PH was not shown, it appears safe to use such therapy if clinically indicated in specific cases.” (Krowka M, et al., A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Iloprost Inhalation in Adults with Abnormal Pulmonary Arterial Pressure and Exercise Limitation Associated with Idiopathic Pulmonary Fibrosis, *Chest* 132:633A (2007) (UTC_PH-ILD_010497) at Abstract.) It is for this reason that experts make treatment decisions on a case-by-case basis. Dr. Nathan also uses Sildenafil to treat PH-ILD patients. (Nathan Dep. Tr. 87:18-89:13; 92:15-20).

Moreover, by comparison, the closest prior art, which does concern administering treprostinil to patients with PH-ILD, demonstrates that treprostinil could be successfully used in patients with PH-ILD to improve exercise capacity, reduce exacerbations, and improve FVC. (*See*

Section III.B *supra*.) As far back as 2009, doctors were treating PH-ILD patients with Tyvaso®, and as Dr. Rothblatt admitted, even UTC knew it worked by 2018. (UTC 2018 Earnings Call at 10.)

4. No Commercial Success

For commercial success, “the asserted commercial success of the product must be due to the merits of the *claimed invention* beyond what was readily available in the prior art.” *J.T. Eaton & Co. v. Atlantic Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997) (emphasis added). “[I]nformation solely on number of units sold is insufficient to establish commercial success.” *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991). Any contention that Tyvaso® has experienced commercial success, without actual evidence beyond sales provided, or establishing a nexus between the claimed inventions and alleged commercial success, is legally insufficient to establish commercial success. *Id.*

UTC cannot establish that sales of Tyvaso® for the indication for the treatment of PH-ILD are due to the merits of the ’327 patent’s claimed invention beyond what was readily available in the prior art. As explained above in Sections III.A-B, treating PH-ILD with inhaled treprostinil was well known in the art long before April 17, 2020. UTC cannot establish a nexus between any alleged success and the claims of the ’327 patent and therefore, UTC cannot establish that any alleged commercial success is due to any claimed aspect of the ’327 patent.

Further, UTC cannot establish that Tyvaso®’s commercial success is due to the inventions claimed in the ’327 patent, because UTC has blocked all competition for treprostinil products for the treatment of PH-ILD. Initially, UTC obtained orphan drug exclusivity for Tyvaso® that prevented additional inhaled treprostinil products from being approved by the FDA and commercialized. UTC continues to seek ways to delay the entry of additional inhaled treprostinil products. On February 20, 2024, UTC filed a Complaint against the FDA to force Liquidia to

make additional submissions to the FDA and thereby delay approval of Liquidia's application. *United Therapeutics Corp. v. FDA*, No. 1:24-cv-0484-JDB, Dkt. 1 (D.D.C. Feb. 20, 2024). Additionally, several companies have sought to make generic treprostinil products, but in each instance, UTC has settled litigation that prevented those companies from marketing their products. *See United Therapeutics Corp. v. Watson Lab's, Inc.*, No. 3:15-cv-05723 (D.N.J. 2015); *United Therapeutics Corp. v. Par Sterile Products, LLC*, No. 3:16-cv-08548 (D.N.J. 2016); *United Therapeutics Corp. v. Par Sterile Products, LLC*, No. 1:16-cv-01066 (D. Del. 2016); *United Therapeutics Corp. v. Actavis Lab's FL, Inc.*, No. 3:16-cv-03642 (D.N.J. 2016); *United Therapeutics Corp. v. Actavis Lab's FL, Inc.*, No. 3:16-cv-01816 (D.N.J. 2016); *United Therapeutics Corp. v. Teva Pharms. USA, Inc.*, No. 3:14-cv-05498 (D.N.J. 2014); *United Therapeutics Corp. v. Sandoz, Inc.*, No. 3:14-cv-05499 (D.N.J. 2014); *United Therapeutics Corp. v. Sandoz, Inc.*, No. 3:13-cv-00316 (D.N.J. 2013); *United Therapeutics Corp. v. Sandoz, Inc.*, No. 3:12-cv-01617 (D.N.J. 2012). Further, UTC has systematically used its patents covering treprostinil, and continues to attempt to obtain new patents, including the '793 patent and '327 patent, to block others from developing and commercializing treprostinil products. *Acorda Therapeutics, Inc. v. Roxane Lab's, Inc.*, 903 F.3d 1310, 1338-39 (Fed. Cir. 2018).

5. Liquidia Does Not Copy Claims 11 and 14 of the '327 Patent

Liquidia's dry powder inhaler is not a "pulsed inhalation device" within the meaning of that term. Liquidia's dry powder inhaler does not generate force or have any electronic or other mechanism that could generate such force. The patient inhales the Yutrepia™ dry powder only through the force generated through her own breath. Accordingly, Liquidia does not copy Asserted Claims 11 and 14 of the '327 patent.

VI. ASSERTED CLAIMS 1, 2, 4, 6-9, AND 14 OF THE '327 PATENT ARE INVALID UNDER 35 U.S.C. § 112

To the extent UTC argues the the Asserted Claims are not invalid under §§ 102 and/or 103, the Asserted Claims of the '327 patent are invalid under 35 U.S.C. § 112 for lack of written description support, lack of enablement, and indefiniteness.

A. The Asserted Claims of the '327 Patent Lack Adequate Written Description

“[T]he test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.” *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). An adequate written description need not in every instance describe an actual reduction to practice but “must nonetheless ‘describe the claimed subject matter in terms that establish that [the applicant] was in possession of the . . . claimed invention, including all of the elements and limitations.’” *University of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 926 (Fed. Cir. 2004) (quoting *Hyatt v. Boone*, 146 F.3d 1348, 1353 (Fed. Cir. 1998)).

1. The Limitation reciting “statistically significant . . . in the patient” is not adequately described

Asserted Claims 2, 4, 9, and 10 of the '327 patent, all dependent claims of Asserted Claim 1, and for Claim 10, dependent Claim 9, all require a “statistically significant [increase/reduction/improvement] ... in the patient.” A POSA would have understood the “the patient” limitation of Asserted Claims 2, 4, 9, and 10 as referencing back to the “a patient” limitation in Asserted Claim 1. As proposed by Liquidia, the terms “a” and “the” mean “one or more than one.” This construction is consistent with the specification of the '327 patent which states that “as used herein and in the appended claims, the singular forms ‘a,’ ‘an,’ and ‘the’ include plural referents unless the context clearly dictates otherwise.” ('327 patent at UTC_PH-ILD_005335 (6:15-17).) Thus, a POSA would have understood the “the patient” term in dependent Asserted Claims 2, 4, 9, and 10 include “one” patient. In other words, a POSA would

have understood that Asserted Claims 2, 4, 9 and 10 of the '327 patent encompasses a method of administering treprostinil to one patient.

As stated above, an adequate written description must allow a POSA to understand that the applicant indeed was “in possession of the ... claimed invention, including all of the elements and limitations.” *University of Rochester*, 358 F.3d at 926. However, a POSA reading the '327 patent would not understand that the applicant possessed the methods of Asserted Claims 2, 4, 9 and 10 with respect to “statistically significant [increases/reductions/improvements]” in a single patient. Rather, a POSA would recognize that a statistically significant change is impossible to achieve when the sample size of the treatment is a single patient. The '327 patent specification does not explain how it is possible to render a “statistically significant [increase/reduction/improvement]” when administering treprostinil to a single patient. Dr. Channick also noted that “it is not possible to determine ‘statistical significance’ from ‘a patient’ as required by Claim 1.” (Channick Decl., ¶130 n.201.) Even UTC’s expert, Dr. Nathan, testified that one “can’t determine statistical significance in a single patient.” (Nathan Dep. Tr. at 71:9-72:10.) Because a POSA would not understand that the inventors possessed the methods of Asserted Claims 2, 4, 9 and 10 for the reasons above, the '327 patent is invalid for lack of written description regarding those claims.

2. The Limitation “FVC” is not adequately described

Asserted Claims 9 and 10 of the '327 patent require an improvement in “forced vital capacity (FVC).” The language of Asserted Claims 9 and 10 do not restrict the meaning of FVC, but POSAs understand FVC to include both % predicted FVC and absolute FVC. Neither the '327 patent’s claims nor specification provide any guidance that would allow a POSA to limit the scope of the claim term “forced vital capacity (FVC)” to just % predicted or absolute FVC. Rather, the specification uses the term FVC to refer to both % predicted and absolute FVC. (*See e.g.*, '327

patent at UTC_PH-ILD_005333 (2:4-52).) Thus, a POSA would have had no reason to construe Asserted Claims 9 and 10 to exclude either % predicted or absolute FVC from its scope.

The '327 patent does provide examples of statistically significant improvements of % predicted FVC. For example, the '327 patent specification provides that treating PH-ILD patients in the INCREASE trial demonstrated a FVC (% predicted) increase of 1.79% ($p=0.01$) at 8 weeks and an increase of 1.80% ($p=0.03$) at 16 weeks. ('327 patent at UTC_PH-ILD_005353 (col. 41, Table 10).) However, the '327 patent does not show any examples of statistically significant improvements of absolute FVC. In the same example, the '327 patent shows FVC improvements of 28.47 ml and 44.40 ml, respectively at 8 weeks and 16 weeks, but those improvements had p-values of 0.35 and 0.21 and thus were not statistically significant. (*Id.*) This has been confirmed by Dr. Nathan, who testified that the INCREASE Study did not see a statistically significant FVC improvement in milliliters. (Nathan Dep. Tr. at 203:6-204:21.) In fact, Dr. Nathan additionally testified that UTC is conducting a subsequent study, TETON, to examine whether patients indeed show an improvement in FVC. (Nathan Dep. Tr. at 117:12-118:17.) Thus, as of the filing date of the '327 patent, a POSA would understand that the inventors were not in possession of the full scope of Asserted Claims 9 and 10.

To the extent that UTC relies on Example 1 and Tables 2–3 in the '327 patent to argue that the '327 patent discloses statistically significant improvements of absolute FVC, UTC is mistaken. Tables 2 and 3 in the '327 patent disclose absolute FVC improvements of 108.18 ml and 168.52 ml at 16 weeks with p-values of 0.0229 and 0.0108, respectively. ('327 patent at UTC_PH-ILD_005344–345 (Tables 2–3, 25:29-43).) However, the data in Tables 2–3 are for subpopulations of the INCREASE Study and are not representative of the entire INCREASE Study population, nor do they represent the scope of PH-ILD patients encompassed by Asserted Claim 1, 9 and 10, which are not limited to certain subpopulations. (*Compare* '327 patent at UTC_PH-

ILD_005344–345 (Tables 2–3) *with* LIQ_PH-ILD_00000216 at LIQ_PH-ILD_00000220–221 (Figures 2-3).) For the reasons discussed in this section, a POSA would not have understood the inventors of the '327 to have possessed the invention of Asserted Claims 9 and 10. Asserted Claims 9 and 10 of the '327 patent therefore lacks adequate written description under 35 U.S.C. § 112.

3. The Limitation “pulsed inhalation device is a dry powder inhaler” is not adequately described

Asserted Claim 14 recites a method of administering inhaled treprostinil “wherein the pulsed inhalation device is a dry powder inhaler.” However, the intrinsic evidence does not adequately describe a “pulsed inhalation device [that] is a dry powder inhaler” and a POSA would not be able to determine that the applicant possessed the invention of Asserted Claim 14 at the time of filing.

The '327 patent specification provides examples of pulsed inhalation devices and dry powder inhalers. However, none of those examples show a “pulsed inhalation device [that] is a dry powder inhaler.” The '327 patent specification points to two examples of a dry powder inhaler, U.S. Patent App. Pub. 2019/0321290 (LIQ_PH-ILD_00101792) and WO2019/237028, but the two references do not include any mention of a “pulsed inhalation device” let alone the term “pulsed.” (See '327 patent at UTC_PH-ILD_005343 (21:6-14 (citing and incorporating by reference WO2019/237028)), UTC_PH-ILD_005355 (46:26-30 (citing U.S. Patent App. Pub. 2019/0321290).) The '327 patent specification also cites and incorporates by reference U.S. Patent App. Pub. 2008/0200449 and U.S. Patent Nos. 9,358,240, 9,339,507, 10,376,525, and 10,716,793 as examples of pulsed inhalation devices. ('327 patent at UTC_PH-ILD_005342 (20:53-57).) However, all of these references merely include the boilerplate language:

The inhalation device can be also a dry powder inhaler. In such case, the respiratory drug is inhaled in solid formulation, usually in the form of a powder with particle size less than 10 micrometers in diameter or less than 5 micrometers in diameter.

- “Subjects having underlying lung disease were treated with inhaled treprostinil over 16 weeks. Subjects initiated inhaled treprostinil or placebo at a dose of 3 breaths (18 mcg) 4 times daily (during waking hours). Study drug doses were maximized throughout the study. Dose escalations (additional 1 breath 4 times daily) could occur up to every 3 days with a target dosing regimen of 9 breaths (54 mcg) 4 times daily and a maximum dose of 12 breaths (72 mcg) 4 times daily, are clinically tolerated.” (’327 patent at UTC_PH-ILD_005343 (22:19-27).)
- “Patients may be treated with inhaled treprostinil up to 15 breaths QID [(4 times daily)] based upon tolerability.” (*Id.* at UTC_PH-ILD_005345 (25:52-53).)
- “Patients were assigned in a 1:1 ratio to receive inhaled treprostinil, administered by means of an ultrasonic, pulsed-delivery nebulizer in up to 12 breaths (total 72 µg) four times daily, or placebo.” (*Id.* (26:41-44).)
- “Inhaled treprostinil (0.6 mg per milliliter) was administered by means of an ultrasonic, pulsed-delivery nebulizer at 6 µg per breath. ... The dose of treprostinil or placebo was adjusted, with dose escalation (an additional 1 breath four times daily) occurring as often as every 3 days, with a target dose of 9 breaths four times daily and a maximum dose of 12 breaths four times daily.” (*Id.* at UTC_PH-ILD_005347 (29:42-51).)

A POSA would glean from this disclosure that the ’327 patent’s dosing experiments were within the range of 3 to 15 breaths of inhaled treprostinil (each breath at 6 µg) administered 4 times daily with dose escalations of an additional 1 breath four times daily occurring as often as every 3 days. However, the ’327 patent proposes a myriad additional treatment methods as “Additional Embodiments” of the invention. For example, the ’327 patent proposes:

- An embodiment where “a single inhalation administration event comprises from 1 to 20 breaths.” (’327 patent at UTC_PH-ILD_005359 (53:18-20).)

- An embodiment where “administration is once, twice, thrice, four times, five times, or six times per day.” (*Id.* (53:37-39).)
- An embodiment where “administration is for a period selected from the group consisting of about 1 day, about 1 day to about 3 days, about 3 days to about 6 days, about 6 days to about 9 days, about 9 days to about 12 days, about 12 days to about 15 days, about 15 days to about 18 days, about 18 days to about 21 days, about 21 days to about 24 days, about 24 days to about 27 days, about 27 days to about 30 days, or about greater than 30 days.” (*Id.* (53:40-48).)

among many other suggested embodiments. The language of Asserted Claim 1 of the '327 patent merely requires that inhaled treprostinil of at least 15 µg up to a maximum tolerated dose be administered in a single administration event with each breath comprising at least 6 µg. Thus, Asserted Claim 1 of the '327 patent could encompass at least 1440 unique treatment regimens²⁷ where a single inhalation administration event ranges from 1 to 20 breaths, administration occurs between once or 6 times per day, and administration occurs for a period of about 1 day to a period greater than 30 days. Because of these 1440 unique treatment regimens, which is much less than the entire universe of treatment regimens suggested by the '327 patent, a POSA would have to undergo undue experimentation to explore the universe of treatment regimens claimed by Asserted Claims 1, 9, and 10 of the '327 patent to determine which treatment regimens, if any, would result in a statistically significant improvement in absolute FVC for the entire PH-ILD treatment

²⁷ One to 20 breaths in a single inhalation administration event provides 20 treatment options for a POSA to choose from. Administration occurring between once or 6 times a day provides 6 treatment options for a POSA to choose from. Administration occurring for a period of about 1 day to a period greater than 30 days provides 12 treatment options for a POSA to choose from. Thus, 1440 ($20 \times 6 \times 12$) unique treatment regimens result just from changing these three treatment variables.

population. *See Amgen*, 598 U.S. at 613–15 (finding that despite the asserted patent disclosing a “roadmap” that taught trial-and-error testing to see if an antibody would meet the claimed functional requirements, the invention failed the enablement requirement because it claimed millions of possible antibodies and necessitated an unreasonable number of trial-and-error tests to ascertain the full scope of the claim).) Thus, Asserted Claims 9 and 10 of the ’327 patent is invalid for lack of enablement.

3. The Limitation “Pulsed Inhalation Device is a Dry Powder Inhaler” Lacks Enablement

As explained in Section VI.A.3 above, the ’327 patent does not provide any examples of nor guidance on of how to achieve a “pulsed inhalation device [that] is a dry powder inhaler.” Drs. Channick and Nathan also could not identify any examples of such a device. (Channick Dep. Tr. at 173:18-175:4; Nathan Dep. Tr. at 131:22-132:19.) Because the ’327 patent leaves the POSA in the dark regarding what a “pulsed inhalation device [that] is a dry powder inhaler” ought to be, Asserted Claim 14 of the ’327 patent is not enabled.

C. The Asserted Claims of the ’327 Patent Are Indefinite

Under 35 U.S.C. § 112, patent claims must “particularly point[] out and distinctly claim[] the subject matter” regarded as the invention. 35 U.S.C. § 112(b). A patent is “invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention.” *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 901 (2014).

1. The Limitations Reciting “Statistically Significant . . . in a Patient” Are Indefinite

As explained above in Section VI.A.1, a POSA would have understood dependent claims 2, 4, 9, and 10 to claim methods of administering treprostinil to one PH-ILD patient in order to achieve a statistically significant change in 6MWD, NT-proBNP levels, or FVC after 8 weeks, 12

weeks, or 16 weeks of administration. Additionally, for the same reasons discussed above in Section VI.A.1, a POSA would recognize that a statistically significant change is impossible to achieve when the sample size of the treatment is a single patient. This impossibility has been recognized by Drs. Channick and Nathan as well. (*See* Channick Decl., ¶130 n.201; Nathan Dep. Tr. at 71:9-72:10.) Because nonsensical or impossible claims are held indefinite under 35 U.S.C. § 112, Asserted Claims 2, 4, 9, and 10 of the '327 patent are invalid as indefinite. (*See Synchronoss Techs., Inc. v. Dropbox, Inc.*, 987 F.3d 1358, 1366-67 (Fed. Cir. 2021).

2. The Limitation “Maximum Tolerated Dose” Is Indefinite

Asserted Claim 1 of the '327 patent requires administering an “effective amount of at least 15 micrograms up to a maximum tolerated dose of treprostinil or a pharmaceutically acceptable salt thereof” to a patient. ('327 patent at UTC_PH-ILD_005359 (cl. 1).) The specification of the '327 patent does not explicitly define “maximum tolerated dose.” UTC proposed that the term means “the highest dose that does not cause unacceptable adverse events.” However, the '327 patent specification does not provide the context that would allow a POSA to determine the scope of that definition. Nor does the '327 patent disclose what constitutes an “unacceptable adverse event” within the context of its specification and claims. The '327 patent discloses numerous adverse events, but none are labeled as “acceptable” or “unacceptable.” Furthermore, without knowing which exact types of adverse events would be “unacceptable,” nor the maximum tolerated dose the unacceptable adverse event would occur at, a POSA would not be able to know with reasonable certainty if Asserted Claim 1 requires stopping administration of inhaled treprostinil at the highest dose that the patient can receive without experiencing adverse effects, or if it requires stopping the patient's dose just before the degree of the adverse effects becomes so severe that treatment must be discontinued. Further, Figure 2 of the '327 patent discloses that 16 of the 163 patients that were administered inhaled treprostinil in the INCREASE study discontinued

treatment after experiencing an adverse event, further confounding what constitutes an “unacceptable adverse event.” (’327 patent at UTC_PH-ILD_005319 (Figure 2).) Thus, under UTC’s proposed construction of “maximum tolerated dose,” a POSA would not have reasonable certainty as to the precise scope of Asserted Claim 1, rendering it indefinite.

VII. THE ASSERTED CLAIMS OF THE ’327 PATENT ARE UNENFORCEABLE

The Asserted Claims of the ’327 patent are unenforceable due to inequitable conduct of Shaun Snader, UTC’s Vice President & Associate General Counsel of Intellectual Property, on behalf of UTC, and UTC’s patent counsel, Stephen Maebius during prosecution of the ’327 patent.

“Inequitable conduct is an equitable defense to patent infringement that, if proved, bars enforcement of a patent.” *In re Rembrandt Techs. LP Pat. Litig.*, 899 F.3d 1254, 1272 (Fed. Cir. 2018) (quoting *Therasense, Inc. v. Becton, Dickinson & Co.*, 649 F.3d 1276, 1285 (Fed. Cir. 2011) (en banc)). “To prevail on the defense of inequitable conduct, the accused infringer must prove that the applicant misrepresented or omitted material information with the specific intent to deceive the PTO.” *Id.* Information is material, for purposes of showing inequitable conduct before the PTO, if a substantial likelihood exists that a reasonable examiner would consider it important in deciding whether to allow the application to issue as a patent. *Fox Indus., Inc. v. Structural Preservation Sys., Inc.*, 922 F.2d 801, 803 (Fed. Cir. 1990); *see also Honeywell Int’l Inc. v. Univ. Avionics Sys. Corp.*, 488 F.3d 982, 1000 (Fed. Cir. 2007).

Inequitable conduct occurs when a patent applicant breaches his or her “duty of candor and good faith” to the U.S. Patent and Trademark Office. 37 C.F.R. § 1.56(a). Intentionally failing to disclose prior art material to the PTO’s determination of patentability constitutes inequitable conduct. *See, e.g., Therasense*, 649 F.3d at 1290–91. An individual’s duty to disclose exists throughout the entire course of application process, up through the date of issuance or abandonment. *Fox Indus.*, 922 F.2d at 803–04.

A. Prosecution of the '327 Patent

The '327 patent issued November 28, 2023 from Application No. 17/233,061, filed April 16, 2021. (*See* '327 patent at UTC_PH-ILD_005310 (Cover).) The '061 application was prosecuted by Mr. Maebius, an attorney at Foley & Lardner LLP, on behalf of the applicant, UTC. (Application Data Sheet (UTC_PH-ILD_009419 at UTC_PH-ILD_009515–9521.)) Mr. Snader, the Vice President and Associate General Counsel of Intellectual Property at UTC, signed the “Power of Attorney to Prosecute Applications Before the USPTO” on behalf of UTC. (Power of Attorney (UTC_PH-ILD_009419 at UTC_PH-ILD_009524).) As such, Mr. Maebius acted on behalf of UTC, with the knowledge and permission of Mr. Snader, during the prosecution of the '061 application.

During prosecution, Mr. Maebius submitted three separate Information Disclosure Statements (“IDS”) to the Patent Office disclosing a total of 472 references. (*See* IDS filed May 12, 2021 (disclosing 136 references) (UTC_PH-ILD_009419 at UTC_PH-ILD_009537–9541); IDS filed September 21, 2021 (disclosing 7 references) (UTC_PH-ILD_009419 at UTC_PH-ILD_009555); IDS filed February 16, 2022 (disclosing 329 references) (UTC_PH-ILD_009419 at UTC_PH-ILD_009616–9632).) Among the 329 references submitted in the third IDS was the IPR Petition for U.S. Patent No. 10,716,793, which had been filed July 1, 2021. (IDS filed Feb. 16, 2022 (UTC_PH-ILD_009419 at UTC_PH-ILD_009629).) Every reference included in the third IDS, filed February 16, 2022, was published prior to the submission date of the second IDS, submitted on September 21, 2021, indicating that they could have been disclosed in the second IDS or even earlier during prosecution.

The original independent claim 1 of the '327 patent was directed to “[a] method of treating a pulmonary hypertension due to a condition which is selected from a chronic lung disease, hypoxia, and a combination thereof[.]” Dependent claim 4 specified that the pulmonary

hypertension being treated was specifically associated with interstitial lung disease. (Original '061 Application, cls. 1, 4 (UTC_PH-ILD_009419 at UTC_PH-ILD_009496).) On March 6, 2023, the Examiner rejected claims 1-16 and 18-26 under 35 U.S.C. § 102(a)(1) as anticipated by five separate references. The Examiner found that claims 1-16 and 18-26 were anticipated by Malinin et al. (WO2015/138423), Zhang et al. (WO2016/205202), Morgans et al. (WO2012/009097), Wade et al. (WO2008/098196) and Bosc et al. (WO2016/176399). (Non-final Rejection (UTC_PH-ILD_009419 at UTC_PH-ILD_009707–09).

On May 10, 2023, Mr. Maebius on behalf of UTC, with the knowledge and permission of Mr. Snader, amended claim 1 as follows:

1. (Currently Amended) A method of improving exercise capacity in a patient having ~~treating a~~ pulmonary hypertension associated with interstitial lung disease ~~due to a condition which is selected from a chronic lung disease, hypoxia and a combination thereof,~~ comprising administering by inhalation to the patient having pulmonary hypertension associated with interstitial lung disease ~~a subject having the pulmonary hypertension due to the condition selected from a chronic lung disease, hypoxia and a combination thereof~~ an effective amount of at least 15 micrograms up to a maximum tolerated dose of treprostinil or a pharmaceutically acceptable salt thereof in a single administration event that comprises an amount of at least 6 micrograms per breath.

(Applicant's Amendment and Remarks from prosecution of the '327 patent, UTC_PH-ILD_009419 at UTC_PH-ILD_009739).

Mr. Maebius remarked that Malinin, Wang, Morgans, and Bosc do not teach or suggest elements of amended claim 1, including the dose, the amount of treprostinil per breath, and the improvement of exercise capacity in a patient with pulmonary hypertension associated with interstitial lung disease. (Applicant's Amendment and Remarks from prosecution of the '327 patent (UTC_PH-ILD_009419 at UTC_PH-ILD_009742–45).)

Mr. Maebius further remarked that Morgans and Bosc teach “nothing regarding administering treprostinil by inhalation[,]” and that “[b]ecause Bosc [and Morgans] teach[]

nothing regarding administering treprostinil by inhalation, Bosc [and Morgans] also teach[] nothing about either treprostinil doses for inhalation or an amount of treprostinil administered per breath. Furthermore, Bosc [and Morgans] teach[] nothing regarding improving exercise capacity in any patient.” (Applicant’s Amendment and Remarks from prosecution of the ’327 patent (UTC_PH-ILD_009419 at UTC_PH-ILD_009744–45). The only remark made by Mr. Maebius regarding the anticipatory reference Wade was that “Wade does not teach or suggest ‘a single administration event that comprises at least 6 micrograms per breath’ as amended claim 1 recites.” (Applicant’s Amendment and Remarks from prosecution of the ’327 patent (UTC_PH-ILD_009419 at UTC_PH-ILD_009744).)

On June 28, 2023, the Examiner issued a Notice of Allowance and stated in the “Reasons for Allowance” that “the methods were not found to be obvious or anticipated by the prior art of record. The prior art does not teach or suggest the methods encompassing compounds substituted in the manner claimed by the Applicant.” (Notice of Allowance (UTC_PH-ILD_009419 at UTC_PH-ILD_009754).) The PTO provided an “Issue Notification” on November 8, 2023, indicating the ’327 patent would issue on November 28, 2023. (Issue Notification (UTC_PH-ILD_009419 at UTC_PH-ILD_009770–771).)

However, as shown below, Mr. Maebius and Mr. Snader, on behalf of UTC, were aware of additional prior art disclosing the limitations discussed in the Examiner’s Non-final Rejection and in UTC’s Amendment and Remarks and did not disclose such prior art to the PTO. Neither Mr. Snader nor Mr. Maebius disclosed UTC’s submissions to the PTAB the *Inter Partes* Review of the ’793 patent (“’793 IPR”), the Institution Decision and Final Written Decision (“FWD”) from the ’793 IPR, any of UTC or Liquidia’s submissions before the District Court of Delaware regarding the ’793 patent, the District Court’s decision finding that the “’793 patent covered all 5 PH WHO Groups, Dr. Martine Rothblatt’s, UTC’s CEO’s, statements regarding PH-ILD made in

Discovery and Liquidia's investigation are ongoing, and Liquidia reserves the right to modify and/or supplement its Initial Invalidity Contentions.

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EXHIBIT 2

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS CORPORATION,)
)
Plaintiff,)
) C.A. No. 20-755-RGA-JLH
v.)
) Volume IV
LIQUIDIA TECHNOLOGIES, INC.,)
)
Defendant.)

J. Caleb Boggs Courthouse
844 North King Street
Wilmington, Delaware

Thursday, March 31, 2022
9:00 a.m.
Bench Trial

BEFORE: THE HONORABLE RICHARD G. ANDREWS, U.S.D.C.J.

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For the Defendants

*** PROCEEDINGS ***

DEPUTY CLERK: All rise. Court is now in
session. Honorable Richard G. Andrews presiding.

THE COURT: Good morning, everyone. Please be
seated.

09:00:14 1 So we're here for the closing arguments and,
09:00:23 2 Mr. Jackson, are you presenting for your side.
09:00:25 3 MR. JACKSON: Yes, Your Honor.
09:00:25 4 THE COURT: And you are -- you're ready?
09:00:27 5 MR. JACKSON: Yes, Your Honor.
09:00:27 6 THE COURT: And, Mr. Sukduang, you're presenting
09:00:30 7 for your side?
09:00:30 8 MR. SUKDUANG: Yes, Your Honor.
09:00:31 9 THE COURT: And you're ready?
09:00:32 10 MR. SUKDUANG: Yes, Your Honor.
09:00:33 11 THE COURT: All right. Well, then, let's go
09:00:36 12 ahead, Mr. Jackson.
09:00:37 13 MR. JACKSON: May I approach?
09:00:39 14 THE COURT: Sure.
09:00:51 15 MR. JACKSON: Good morning, Your Honor.
09:00:57 16 THE COURT: All right. Good morning,
09:00:58 17 Mr. Jackson.
09:00:59 18 MR. JACKSON: First on behalf of United
09:01:00 19 Therapeutics, I'd like to thank you for your time and
09:01:02 20 attention as we put in the evidence over the past several
09:01:05 21 days, including a number of individuals who testified by
09:01:09 22 deposition. Not always great to watch a video.
09:01:13 23 So, this case, obviously, involves two patents,
09:01:16 24 the '066 and the '793. I'm going to take them one by one.
09:01:19 25 '066 is the synthesis patent, and the '793 is the treatment

10:02:59 1 inducement, and no actual evidence that a hemodynamic change
10:03:04 2 results in therapeutic efficacy.

10:03:07 3 And again, I circle back to the testimony of
10:03:09 4 Dr. Hill. There are patients that receive drugs like
10:03:13 5 Treprostinil, that obtain a positive hemodynamic effect.
10:03:18 6 When I say positive, it's -- you want to see the pressure
10:03:21 7 change. Those patients, it's the first study, those
10:03:25 8 patients got sicker and some died. That that establishes
10:03:30 9 that a hemodynamic effect does not equate to therapeutic.

10:03:36 10 So, Your Honor, I know I went over my time. I
10:03:39 11 appreciate the indulgence. I do have one more thing to say.
10:03:42 12 We do appreciate your time and your staff. Liquidia
10:03:45 13 appreciates your time and your staff. I have a lot of
10:03:47 14 members on my team that I have literally not met until we
10:03:51 15 showed up for trial this week because of COVID. And we have
10:03:54 16 several members of our team that this was the first time
10:03:57 17 that they had a standup role at trial. And we appreciate
10:04:01 18 the opportunity that you provided to them to allow them to
10:04:04 19 speak, and I know Liquidia does. And we appreciate your
10:04:07 20 time. Thank you.

10:04:08 21 THE COURT: All right. Thank you. Let me just
10:04:10 22 follow up on one or two things with you.

10:04:12 23 So I presume the reason why Liquidia wanted to
10:04:17 24 get in this business is because they believe that the label
10:04:22 25 instructions do recommend a therapeutically effective

10:04:26 1 treatment; right?

10:04:28 2 MR. SUKDUANG: Yes. Well, the FDA -- you could
10:04:30 3 not sell the drug if it wasn't therapeutically effective.

10:04:32 4 THE COURT: Right. And I take it that if they
10:04:37 5 are instructing through the label to take this -- to inhale
10:04:46 6 this three or four different times a day -- which is what
10:04:49 7 the label says; right?

10:04:51 8 MR. SUKDUANG: Yes.

10:04:52 9 THE COURT: Then that's necessarily, if you
10:04:56 10 break the day down into four different parts, telling them
10:04:59 11 to do it, you know, once in the morning, once in the
10:05:01 12 afternoon, once in the evening, and once before bed or
10:05:04 13 whatever it works out to, that telling them to do it four
10:05:08 14 times is also if you measure it in -- that each time they're
10:05:15 15 also telling them do it each individual time; right?

10:05:19 16 MR. SUKDUANG: Yeah, you have to take it four
10:05:21 17 times a day or three to five times a day depending on how
10:05:25 18 you -- patients need different amounts, so it could be three
10:05:28 19 times or five times.

10:05:29 20 THE COURT: Right. But the point is, you now
10:05:33 21 you know, if I tell you to take four pills a day, I'm
10:05:37 22 necessarily also telling you to take a pill; right?

10:05:40 23 MR. SUKDUANG: Yes, but I'm telling you to take
10:05:42 24 four pills because if I tell you to take one pill, it's not
10:05:45 25 going to work.

10:05:46 1 THE COURT: So, in -- -- hold on a second. I
10:05:55 2 lost my thought.

10:05:56 3 And so, the -- it's not the case that the patent
10:06:01 4 claims are limited to taking one therapeutically effective
10:06:09 5 single-event dose; right?

10:06:10 6 MR. SUKDUANG: It is. When you look at the
10:06:12 7 claim, when you look at the claim, it's a single-event dose
10:06:15 8 is therapeutically effective.

10:06:17 9 THE COURT: Well --

10:06:17 10 MR. SUKDUANG: And you look --

10:06:18 11 THE COURT: -- that's true, but it doesn't
10:06:19 12 prevent you from taking multiple single effective doses;
10:06:22 13 right?

10:06:23 14 MR. SUKDUANG: I think when you look at the
10:06:24 15 claim, and you look at the specification, that's the
10:06:27 16 instruction. And the reason for that is twofold.

10:06:30 17 When you look at the examples, Examples 1 and 2,
10:06:33 18 Examples 1 and 2 are only a single dose, not multiple
10:06:40 19 dosing. And Examples 1 and 2, look at hemodynamics and say
10:06:44 20 on a single dose, that's what you need. The patent also has
10:06:50 21 that language, and I think you saw it today and you saw it
10:06:52 22 during some testimony that says you can use it a single time
10:06:55 23 or multiple times per day; right?

10:06:57 24 THE COURT: Right.

10:07:00 25 MR. SUKDUANG: That's indication in the language

10:07:01 1 of the patent that the inventors knew how to say -- how to
10:07:04 2 teach how to take something once or how to take things
10:07:07 3 multiple times, but they chose not --

10:07:09 4 THE COURT: But the patent itself --

10:07:10 5 MR. SUKDUANG: I'm sorry.

10:07:11 6 THE COURT: But the patent itself says a method
10:07:13 7 of treating by administering a therapeutically effective
10:07:19 8 single-event dose.

10:07:20 9 MR. SUKDUANG: Correct.

10:07:20 10 THE COURT: Doesn't that mean one or more?

10:07:22 11 MR. SUKDUANG: No. "A" is one. There's case
10:07:24 12 law and we can brief that for you. "A" is one. There's
10:07:27 13 case law that says one or more. There's case law that
10:07:30 14 says --

10:07:31 15 THE COURT: Yeah, but one or more is simply the
10:07:34 16 prefer reading; right?

10:07:35 17 MR. SUKDUANG: Of "A"?

10:07:36 18 THE COURT: Yes.

10:07:36 19 MR. SUKDUANG: I'm not sure that's the case.

10:07:38 20 THE COURT: I am sure that's the case.

10:07:40 21 MR. SUKDUANG: Okay. Yes. But when you look at
10:07:41 22 "A," you have to look at the rest of the patent. Look at
10:07:44 23 the examples. The examples are single dose studies. Single
10:07:47 24 dose. And they got a patent. They got a patent on a method
10:07:51 25 of treating --

10:07:52 1 THE COURT: Although -- you say examples, but as
10:07:55 2 you as also pointed out and as your opponents pointed out,
10:07:58 3 the actual written description says a single dose or
10:08:01 4 multiple dose.

10:08:02 5 MR. SUKDUANG: That's -- yeah, you can take a
10:08:03 6 single dose or multiple dose.

10:08:05 7 THE COURT: So, they could, notwithstanding the
10:08:08 8 examples because we know claims are not limited to examples,
10:08:12 9 they could claim one or more doses?

10:08:15 10 MR. SUKDUANG: They could have, but they didn't.
10:08:17 11 I mean, that's the problem that we're having. I understand
10:08:20 12 the issue, Your Honor.

10:08:20 13 THE COURT: You're going to have to convince me
10:08:23 14 of that.

10:08:23 15 MR. SUKDUANG: I understand the issue, Your
10:08:25 16 Honor.

10:08:25 17 THE COURT: Hold on. Let me see if there's
10:08:27 18 something else that I want to ask you about.

10:08:30 19 So, I hate to be dense on this point, but your
10:08:35 20 argument in terms of the product being the same for the
10:08:50 21 product-by-process claims, which I think are Claims 6 and 9;
10:08:50 22 right?

10:08:57 23 MR. SUKDUANG: The product-by-process claims are
10:08:59 24 Claims 1 -- Claim 1 is a product-by-process claim I think
10:09:04 25 all asserted claims except Claim 8 a product-by-process

10:09:08 1 claim.

10:09:10 2 THE COURT: Hold on just a minute.

10:09:17 3 Okay. So, just going to Claim 8, one of the
10:09:22 4 points that your opponent said was that because I knocked
10:09:28 5 out the indefiniteness argument, that there's no actual --

10:09:35 6 MR. SUKDUANG: Invalidity.

10:09:36 7 THE COURT: -- invalidity -- thank you --
10:09:38 8 argument still standing on that. Is that right?

10:09:44 9 MR. SUKDUANG: Right. So now with respect to
10:09:45 10 Claim 8, based on your ruling it's the storage limitation,
10:09:49 11 and the storage -- because Claim 8, also like Claim 6,
10:09:52 12 includes the storage limitation. It says it has to be
10:09:56 13 stable at ambient temperature and then stored before you
10:09:58 14 make the pharmaceutical product.

10:10:00 15 THE COURT: Right. So in other words, what you
10:10:02 16 say is the written description, then, presumably --

10:10:05 17 MR. SUKDUANG: No. No, Your Honor. It's the
10:10:07 18 non-infringement now on Claim 8.

10:10:09 19 THE COURT: Oh, okay. All right. So there's no
10:10:11 20 invalidity claim on Claim 8?

10:10:12 21 MR. SUKDUANG: Correct. It's non-infringement
10:10:14 22 of Claim 8.

10:10:14 23 THE COURT: Got it. Okay. Thank you.

10:10:26 24 And so, on the -- and just to go back, I think
10:10:32 25 maybe I asked you about this while you were arguing, but --

10:10:40 1 your written description arguments relating to impurities
10:10:48 2 is, essentially, they don't provide any data that shows what
10:10:53 3 they say is happening is true; is that right?

10:10:56 4 MR. SUKDUANG: It's twofold. It's, one, there's
10:11:00 5 no data to do the actual comparison; right? So it's not
10:11:03 6 just a matter of is it true. The claim requires comparison.

10:11:07 7 THE COURT: Or that they have it.

10:11:09 8 MR. SUKDUANG: Or that they have it, they have
10:11:11 9 possession. So there's no data that they have possession of
10:11:14 10 it. And then when you look at the patent as a whole, when
10:11:17 11 you look at what they did, it's not just that there's no
10:11:20 12 data. It's that they -- there's just never a comparison.
10:11:24 13 They never say compare starting batch to final
10:11:27 14 pharmaceutical composition. That only shows up in the
10:11:30 15 claim.

10:11:31 16 So, and the reason for that is because when you
10:11:35 17 look at the process -- and I bring up inventor testimony not
10:11:38 18 in terms of what they did but just to explain what the
10:11:40 19 invention was. I'm sorry. What they did was eliminate
10:11:47 20 column chromatography. So when you eliminate column
10:11:51 21 chromatography, you have to eventually purify the product.
10:11:54 22 And what they did was they added a salt step at the end. So
10:11:58 23 you made Treprostinil, and then in the example of the
10:12:01 24 patents, they used a diethanolamine base to make
10:12:04 25 Treprostinil diethanolamine salt. And the patent says when

10:12:07 1 you perform the carbon and salt treatment steps, you can
10:12:10 2 remove the impurities at the very end.

10:12:12 3 So when you look at the process itself, as you
10:12:15 4 flow through the examples, Example 1, 2, 3, Example 1 is
10:12:20 5 making -- is alkylating the BTO.

10:12:24 6 Example 2 is you take that product, and in the
10:12:27 7 patent it's called the benzidine nitrile. You take that
10:12:30 8 benzidine nitrile, and you conduct hydrolysis to form
10:12:35 9 Treprostinil.

10:12:35 10 When you read the examples, the end of Example 1
10:12:38 11 says you take the crude material and you move it to the next
10:12:42 12 step. And then when you look at the end of Example 2, it
10:12:45 13 says you take that crude material and you move to the next
10:12:48 14 step, which is Step 3, which is the formation of the
10:12:52 15 diethanolamine salt or any salt, but the example is the
10:12:55 16 diethanolamine salt.

10:12:56 17 So, when you look at the process, not only is
10:13:00 18 there no data, but I view it as kind of like a one-flow
10:13:06 19 process that you take a solution out of Step 1, and you take
10:13:11 20 that solution and you use it as part of Step 2, and you take
10:13:14 21 that solution and then you use it as part of Step 3 or
10:13:17 22 Example 3 to make the salt.

10:13:19 23 So it's twofold. No data. They didn't actually
10:13:23 24 measure data because they didn't have to. And, two, in how
10:13:27 25 in how you do the process, according to UT, they don't need

1 I hereby certify the foregoing is a true and
2 accurate transcript from my stenographic notes in the
3 proceeding.

4 /s/ Heather M. Triozzi
5 Certified Merit and Real-Time Reporter
6 U.S. District Court.
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EXHIBIT 3

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TYVASO safely and effectively. See full prescribing information for TYVASO.

TYVASO (treprostinil) inhalation solution

Initial U.S. Approval: 2002

For Oral Inhalation Only

INDICATIONS AND USAGE

Tyvaso is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in patients with NYHA Class III symptoms, to increase walk distance. (1)

DOSAGE AND ADMINISTRATION

- Use only with the Tyvaso Inhalation System. (2.1)
- Administer undiluted, as supplied. A single breath of Tyvaso delivers approximately 6 mcg of treprostinil. (2.1)
- Administer in 4 separate treatment sessions each day approximately four hours apart, during waking hours. (2.1)
- Initial dosage: 3 breaths [18 mcg] per treatment session. If 3 breaths are not tolerated, reduce to 1 or 2 breaths. (2.1)
- Dosage should be increased by an additional 3 breaths at approximately 1-2 week intervals, if tolerated. (2.1)
- Titrate to target maintenance dosage of 9 breaths or 54 mcg per treatment session as tolerated. (2.1)

DOSAGE FORMS AND STRENGTHS

Sterile solution for oral inhalation: 2.9 mL ampule containing 1.74 mg treprostinil (0.6 mg per mL). (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Safety and efficacy have not been established in patients with significant underlying lung disease (such as asthma or chronic obstructive pulmonary disease). (5.1)
- In patients with low systemic arterial pressure, Tyvaso may cause symptomatic hypotension. (5.2)
- Tyvaso may increase the risk of bleeding, particularly in patients receiving anticoagulants. (5.4, 7.2)
- Tyvaso dosage adjustments may be necessary if inhibitors or inducers of CYP2C8 are added or withdrawn. (5.5, 7.5)
- Hepatic or renal insufficiency may increase exposure and decrease tolerability. (2.2, 2.3, 5.3)

ADVERSE REACTIONS

Most common adverse reactions ($\geq 10\%$) are cough, headache, nausea, dizziness, flushing, throat irritation, pharyngolaryngeal pain and diarrhea. (6)

To report SUSPECTED ADVERSE REACTIONS, contact United Therapeutics Corp. at 1-866-458-6479 or via e-mail at drugsafety@unither.com, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Concomitant diuretics, antihypertensives or other vasodilators may increase the risk of systemic hypotension. (7.1)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Tyvaso should be used only if clearly needed. (8.1)
- Nursing women: Caution should be exercised when administered to a nursing woman. (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

*Sections or subsections omitted from the full prescribing information are not listed.

Revised: [July/2009]

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FULL PRESCRIBING INFORMATION

Tyvaso™ (treprostinil) inhalation solution

For Oral Inhalation Only

1 INDICATIONS AND USAGE

Tyvaso is indicated to increase walk distance in patients with WHO Group I pulmonary arterial hypertension and NYHA Class III symptoms. The effects diminish over the minimum recommended dosing interval of 4 hours; treatment timing can be adjusted for planned activities.

While there are long-term data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil has been on a background of bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase type 5 inhibitor). The controlled clinical experience was limited to 12 weeks in duration [*see Clinical Studies (14)*].

2 DOSAGE AND ADMINISTRATION

2.1 Usual Dosage in Adults

Tyvaso is intended for oral inhalation using the Tyvaso Inhalation System, which consists of the Optineb-ir Model ON-100/7 (an ultrasonic, pulsed-delivery device) and its accessories.

Tyvaso is dosed in 4 separate, equally spaced treatment sessions per day, during waking hours. The treatment sessions should be approximately 4 hours apart.

Initial Dosage:

Therapy should begin with 3 breaths of Tyvaso (18 mcg of treprostinil), per treatment session, 4 times daily. If 3 breaths are not tolerated, reduce to 1 or 2 breaths and subsequently increase to 3 breaths, as tolerated.

Maintenance Dosage:

Dosage should be increased by an additional 3 breaths at approximately 1-2 week intervals, if tolerated, until the target dose of 9 breaths (54 mcg of treprostinil) is reached per treatment session, 4 times daily. If adverse effects preclude titration to target dose, Tyvaso should be continued at the highest tolerated dose.

If a scheduled treatment session is missed or interrupted, therapy should be resumed as soon as possible at the usual dose.

The maximum recommended dosage is 9 breaths per treatment session, 4 times daily.

2.2 Patients with Hepatic Insufficiency

Plasma clearance of treprostinil is reduced in patients with hepatic insufficiency. Patients with hepatic insufficiency may therefore be at increased risk of dose-dependent adverse reactions because of an increase in systemic exposure [*see Warnings and Precautions (5.3), Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*].

2.3 Patients with Renal Insufficiency

Plasma clearance of treprostinil may be reduced in patients with renal insufficiency, since treprostinil and its metabolites are excreted mainly through the urinary route. Patients with renal insufficiency may therefore be at increased risk of dose-dependent adverse reactions [*see Warnings and Precautions (5.3), Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)*].

2.4 Administration

Tyvaso must be used only with the Tyvaso Inhalation System. Patients should follow the instructions for use for operation of the Tyvaso Inhalation System and for daily cleaning of the device components after the last treatment session of the day. To avoid potential interruptions in drug delivery because of equipment malfunction, patients should have access to a back-up Optineb-ir device.

Do not mix Tyvaso with other medications in the Optineb-ir device. Compatibility of Tyvaso with other medications has not been studied.

The Tyvaso Inhalation System should be prepared for use each day according to the instructions for use. One ampule of Tyvaso contains a sufficient volume of medication for all 4 treatment sessions in a single day. Prior to the first treatment session, the patient should twist the top off a single Tyvaso ampule and squeeze the entire contents into the medicine cup. Between each of the 4 daily treatment sessions, the device should be capped and stored upright with the remaining medication inside.

At the end of each day, the medicine cup and any remaining medication must be discarded. The device must be cleaned each day according to the instructions for use.

Avoid skin or eye contact with Tyvaso solution. Do not orally ingest the Tyvaso solution.

3 DOSAGE FORMS AND STRENGTHS

Sterile solution for oral inhalation: 2.9 mL ampule containing 1.74 mg of treprostinil (0.6 mg per mL).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Patients with Pulmonary Disease or Pulmonary Infections

The safety and efficacy of Tyvaso have not been established in patients with significant underlying lung disease (e.g., asthma or chronic obstructive pulmonary disease). Patients with acute pulmonary infections should be carefully monitored to detect any worsening of lung disease and loss of drug effect.

5.2 Risk of Symptomatic Hypotension

Treprostinil is a pulmonary and systemic vasodilator. In patients with low systemic arterial pressure, treatment with Tyvaso may produce symptomatic hypotension.

5.3 Patients with Hepatic or Renal Insufficiency

Titrate slowly in patients with hepatic or renal insufficiency, because such patients will likely be exposed to greater systemic concentrations relative to patients with normal hepatic or renal function [*see Dosage and Administration (2.2, 2.3), Use in Specific Populations (8.6, 8.7) and Clinical Pharmacology (12.3)*].

5.4 Risk of Bleeding

Since Tyvaso inhibits platelet aggregation, there may be an increased risk of bleeding, particularly among patients receiving anticoagulant therapy.

5.5 Effect of Other Drugs on Treprostinil

Co-administration of a cytochrome P450 (CYP) 2C8 enzyme inhibitor (e.g., gemfibrozil) may increase exposure (both C_{max} and AUC) to treprostinil. Co-administration of a CYP2C8 enzyme inducer (e.g., rifampin) may decrease exposure to treprostinil. Increased exposure is likely to increase adverse events associated with treprostinil administration, whereas decreased exposure is likely to reduce clinical effectiveness [*see Drug Interactions (7.5) and Clinical Pharmacology (12.3)*].

6 ADVERSE REACTIONS

The following potential adverse reactions are described in Warnings and Precautions (5):

- Decrease in systemic blood pressure [*see Warnings and Precautions (5.2)*].
- Bleeding [*see Warnings and Precautions (5.4)*].

6.1 Adverse Reactions Identified in Clinical Trials

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In a 12-week placebo-controlled study (TRIUMPH I) of 235 patients with PAH (WHO Group I and nearly all NYHA Functional Class III), the most commonly reported adverse reactions on Tyvaso included: cough and throat irritation; headache, gastrointestinal effects, muscle, jaw or bone pain, flushing and syncope. Table 1 lists the adverse reactions that occurred at a rate of at least 4% and were more frequent in patients treated with Tyvaso than with placebo.

Table 1: Adverse Events in $\geq 4\%$ of PAH Patients Receiving Tyvaso and More Frequent* than Placebo		
Adverse Event	Treatment n (%)	
	Tyvaso n = 115	Placebo n = 120
Cough	62 (54)	35 (29)
Headache	47 (41)	27 (23)
Throat Irritation / Pharyngolaryngeal Pain	29 (25)	17 (14)
Nausea	22 (19)	13 (11)
Flushing	17 (15)	1 (<1)
Syncope	7 (6)	1 (<1)

*More than 3% greater than placebo

The safety of Tyvaso was also studied in a long-term, open-label extension study in which 206 patients were dosed for a mean duration of one year. The adverse events during this chronic dosing study were qualitatively similar to those observed in the 12-week placebo controlled trial.

Adverse Events Associated with Route of Administration

Adverse events in the treated group during the double-blind and open-label phase reflecting irritation to the respiratory tract included: cough, throat irritation, pharyngeal pain, epistaxis, hemoptysis and wheezing. Serious adverse events during the open-label portion of the study included pneumonia in 8 subjects. There were three serious episodes of hemoptysis (one fatal) noted during the open-label experience.

7 DRUG INTERACTIONS

Pharmacokinetic/pharmacodynamic interaction studies have not been conducted with inhaled treprostinil (Tyvaso); however, some of such studies have been conducted with orally (treprostinil diethanolamine) and subcutaneously administered treprostinil (Remodulin®).

Pharmacodynamics

7.1 Antihypertensive Agents or Other Vasodilators

Concomitant administration of Tyvaso with diuretics, antihypertensive agents or other vasodilators may increase the risk of symptomatic hypotension.

7.2 Anticoagulants

Since treprostinil inhibits platelet aggregation, there may be an increased risk of bleeding, particularly among patients receiving anticoagulants.

Pharmacokinetics

7.3 Bosentan

In a human pharmacokinetic study conducted with bosentan (250 mg/day) and an oral formulation of treprostinil (treprostinil diethanolamine), no pharmacokinetic interactions between treprostinil and bosentan were observed.

7.4 Sildenafil

In a human pharmacokinetic study conducted with sildenafil (60 mg/day) and an oral formulation of treprostinil (treprostinil diethanolamine), no pharmacokinetic interactions between treprostinil and sildenafil were observed.

7.5 Effect of Cytochrome P450 Inhibitors and Inducers

In vitro studies of human hepatic microsomes showed that treprostinil does not inhibit cytochrome P450 (CYP) isoenzymes CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A. Additionally, treprostinil does not induce cytochrome P450 isoenzymes CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A.

Human pharmacokinetic studies with an oral formulation of treprostinil (treprostinil diethanolamine) indicated that co-administration of the cytochrome P450 (CYP) 2C8 enzyme inhibitor gemfibrozil increases exposure (both C_{max} and AUC) to treprostinil. Co-administration of the CYP2C8 enzyme inducer rifampin decreases exposure to treprostinil. It is unclear if the safety and efficacy of treprostinil by the inhalation route are altered by inhibitors or inducers of CYP2C8 [*see Warnings and Precautions (5.5)*].

7.6 Effect of Other Drugs on Treprostinil

Drug interaction studies have been carried out with treprostinil (oral or subcutaneous) co-administered with acetaminophen (4 g/day), warfarin (25 mg/day), and fluconazole (200 mg/day), respectively in healthy volunteers. These studies did not show a clinically significant effect on the pharmacokinetics of treprostinil. Treprostinil does not affect the pharmacokinetics or pharmacodynamics of warfarin. The pharmacokinetics of R- and S- warfarin and the INR in healthy subjects given a single 25 mg dose of warfarin were unaffected by continuous subcutaneous infusion of treprostinil at an infusion rate of 10 ng/kg/min.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well controlled studies with Tyvaso in pregnant women. Animal reproduction studies have not been conducted with treprostinil administered by the inhalation route. However, studies in pregnant rabbits using continuous subcutaneous (sc) infusions of treprostinil sodium at infusion rates higher than the recommended human sc infusion rate resulted in an increased incidence of fetal skeletal variations associated with maternal toxicity [see *Developmental Toxicity (13.3)*]. Animal reproduction studies are not always predictive of human response; Tyvaso should be used during pregnancy only if clearly needed.

8.2 Labor and Delivery

No treprostinil treatment-related effects on labor and delivery were seen in animal studies. The effect of treprostinil on labor and delivery in humans is unknown.

8.3 Nursing Mothers

It is not known whether treprostinil is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when treprostinil is administered to nursing women.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Clinical studies of Tyvaso did not include patients younger than 18 years to determine whether they respond differently from older patients.

8.5 Geriatric Use

Clinical studies of Tyvaso did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of hepatic, renal, or cardiac dysfunction, and of concomitant diseases or other drug therapy.

8.6 Patients with Hepatic Insufficiency

Plasma clearance of treprostinil, delivered subcutaneously, was reduced up to 80% in subjects with mild-to-moderate hepatic insufficiency. Uptitrate slowly when treating patients with hepatic insufficiency because of the risk of an increase in systemic exposure which may lead to an increase in dose-dependent adverse effects. Treprostinil has not been studied in patients with severe hepatic insufficiency [see *Clinical Pharmacology (12.3)*, *Dosage and Administration (2.2)* and *Warnings and Precautions (5.3)*].

8.7 Patients with Renal Insufficiency

No studies have been performed in patients with renal insufficiency. Since treprostinil and its metabolites are excreted mainly through the urinary route, patients with renal insufficiency may have decreased clearance of the drug and its metabolites and consequently, dose-related adverse outcomes may be more frequent [see *Clinical Pharmacology (12.3)*, *Dosage and Administration (2.3)* and *Warnings and Precautions (5.3)*].

10 OVERDOSAGE

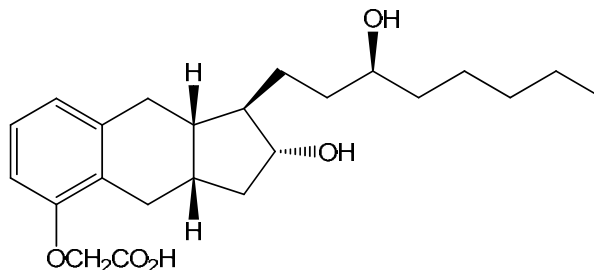
In general, symptoms of overdose with Tyvaso include flushing, headache, hypotension, nausea, vomiting, and diarrhea. Provide general supportive care until the symptoms of overdose have resolved.

11 DESCRIPTION

Tyvaso is a sterile formulation of treprostinil intended for administration by oral inhalation using the Optineb-ir device. Tyvaso is supplied in 2.9 mL low density polyethylene (LDPE) ampules, containing 1.74 mg treprostinil (0.6 mg/mL). Each ampule also contains 18.9 mg sodium chloride, 18.3 mg sodium citrate, 0.58 mg sodium hydroxide, 11.7 mg 1 N hydrochloric acid, and water for injection. Sodium hydroxide and hydrochloric acid may be added to adjust pH between 6.0 and 7.2.

Treprostinil is (1R,2R,3aS,9aS)-[[2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]acetic acid. Treprostinil has a molecular weight of 390.51 and a molecular formula of C₂₃H₃₄O₅.

The structural formula of treprostinil is:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Treprostinil is a prostacyclin analogue. The major pharmacologic actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation.

12.2 Pharmacodynamics

In a clinical trial of 240 healthy volunteers, single doses of Tyvaso 54 mcg (the target maintenance dose per session) and 84 mcg (supratherapeutic inhalation dose) prolonged the corrected QTc interval by approximately 10 ms. The QTc effect dissipated rapidly as the concentration of treprostinil decreased.

12.3 Pharmacokinetics

Pharmacokinetic information for single doses of inhaled treprostinil was obtained in healthy volunteers in three separate studies. Treprostinil systemic exposure (AUC and C_{max}) post-inhalation was shown to be proportional to the doses administered (18 mcg – 90 mcg).

Absorption and Distribution

In a three-period crossover study, the bioavailability of two single doses of Tyvaso (18 mcg and 36 mcg) was compared with that of intravenous treprostinil in 18 healthy volunteers. Mean estimates of the

absolute systemic bioavailability of treprostinil after inhalation were approximately 64% (18 mcg) and 72% (36 mcg).

Treprostinil plasma exposure data were obtained from two studies at the target maintenance dose, 54 mcg. The mean C_{\max} at the target dose was 0.91 and 1.32 ng/mL with corresponding mean T_{\max} of 0.25 and 0.12 hr, respectively. The mean AUC for the 54 mcg dose was 0.81 and 0.97 hr•ng/mL, respectively.

Following parenteral infusion, the apparent steady state volume of distribution (V_{ss}) of treprostinil is approximately 14 L/70 kg ideal body weight.

In vitro treprostinil is 91% bound to human plasma proteins over the 330-10,000 mcg/L concentration range.

Metabolism and Excretion

Of subcutaneously administered treprostinil, only 4% is excreted unchanged in urine. Treprostinil is substantially metabolized by the liver, primarily by CYP2C8. Metabolites are excreted in urine (79%) and feces (13%) over 10 days. Five apparently inactive metabolites were detected in the urine, each accounting for 10-15% of the dose administered. Four of the metabolites are products of oxidation of the 3-hydroxyoctyl side chain and one is a glucuroconjugated derivative (treprostinil glucuronide).

The elimination of treprostinil (following subcutaneous administration of treprostinil) is biphasic, with a terminal elimination half-life of approximately 4 hours using a two compartment model.

Special Populations

Hepatic Insufficiency

Plasma clearance of treprostinil, delivered subcutaneously, was reduced up to 80% in subjects presenting with mild-to-moderate hepatic insufficiency. Treprostinil has not been studied in patients with severe hepatic insufficiency [see *Dosage and Administration* (2.2), *Warnings and Precautions* (5.3) and *Use in Specific Populations* (8.6)].

Renal Insufficiency

No studies have been performed in patients with renal insufficiency; therefore, since treprostinil and its metabolites are excreted mainly through the urinary route, there is the potential for an increase in both parent drug and its metabolites and an increase in systemic exposure [see *Dosage and Administration* (2.3), *Warnings and Precautions* (5.3) and *Use in Specific Populations* (8.7)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies have not been performed to evaluate the carcinogenic potential of treprostinil. In vitro and in vivo genetic toxicology studies did not demonstrate any mutagenic or clastogenic effects of treprostinil. Treprostinil sodium did not affect fertility or mating performance of male or female rats given continuous subcutaneous (sc) infusions at rates of up to 450 ng treprostinil/kg/min [about 59 times the recommended starting human sc infusion rate (1.25 ng/kg/min) and 8 times the average rate (9.3 ng/kg/min) achieved in clinical trials, on a ng/m^2 basis]. In this study, males were dosed from 10 weeks prior to mating and through the 2-week mating period. Females were dosed from 2 weeks prior to mating until gestational day 6.

13.3 Developmental Toxicity

In pregnant rats, continuous sc infusions of treprostinil sodium during organogenesis and late gestational development, at rates as high as 900 ng treprostinil/kg/min (about 117 times the recommended starting human sc infusion rate and about 16 times the average rate achieved in clinical trials, on a ng/m^2 basis), resulted in no evidence of harm to the fetus. In pregnant rabbits, effects of continuous sc infusions of treprostinil during organogenesis were limited to an increased incidence of fetal skeletal variations (bilateral full rib or right rudimentary rib on lumbar vertebra 1) associated with maternal toxicity (reduction in body weight and food consumption) at an infusion rate of 150 ng treprostinil/kg/min (about 41 times the starting human sc infusion rate and 5 times the average rate achieved in clinical trials, on a ng/m^2 basis).

13.4 Inhalational Toxicity

Rats and dogs that received daily administrations of treprostinil by inhalation for 3 months developed respiratory tract lesions (respiratory epithelial degeneration, goblet cell hyperplasia/hypertrophy, epithelial ulceration, squamous epithelial degeneration and necrosis, and lung hemorrhage). Some of the same lesions seen in animals sacrificed at the end of treatment (larynx, lung and nasal cavity lesions in rats, and lesions of the larynx in dogs) were also observed in animals sacrificed after a 4-week recovery period. Rats also developed cardiac changes (degeneration/fibrosis). A no-effect dose level for these effects was not demonstrated in rats (doses as low as 7 $\mu\text{g}/\text{kg}/\text{day}$ were administered); whereas 107 $\mu\text{g}/\text{kg}/\text{day}$ was a no-effect dose level in dogs.

14 CLINICAL STUDIES

TRIUMPH I, was a 12-week, randomized, double-blind, placebo-controlled multi-center study of patients with PAH. The study population included 235 clinically stable subjects with pulmonary arterial hypertension (WHO Group I), nearly all with NYHA Class III symptoms who were receiving either bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase-5 inhibitor) for at least three months prior to study initiation. Concomitant therapy also could have included anticoagulants, other vasodilators (e.g., calcium channel blockers), diuretics, oxygen, and digitalis, but not a prostacyclin. These patients were administered either placebo or Tyvaso in four daily treatment sessions with a target dose of 9 breaths (54 mcg) per session over the course of the 12-week study. Patients were predominantly female (82%), had the origin of PAH as idiopathic/familial (56%), secondary to collagen vascular disease (33%) or secondary to HIV or previous use of anorexigens (12%); bosentan was the concomitant oral medication in 70% of those enrolled, sildenafil in 30%.

The primary efficacy endpoint of the trial was the change in six-minute walk distance (6MWD) relative to baseline at 12 weeks. 6MWD was measured at peak exposure (between 10 and 60 minutes after dosing), and 3-5 hours after bosentan or 0.5-2 hours after sildenafil. Patients receiving Tyvaso had a placebo-corrected median change from baseline in peak 6MWD of 20 meters at Week 12 ($p < 0.001$). The distribution of these 6MWD changes from baseline at Week 12 were plotted across the range of observed values (Figure 1). 6MWD measured at trough exposure (defined as measurement of 6MWD at least 4 hours after dosing) improved by 14 meters. There were no placebo-controlled 6MWD assessments made after 12 weeks.

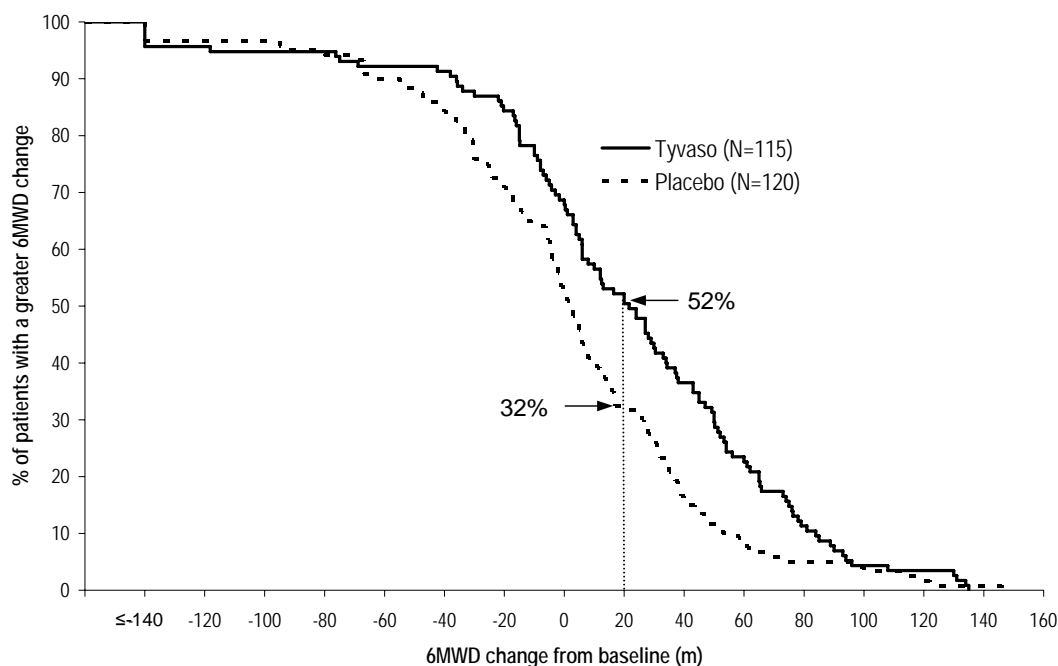


Figure 1: Distributions of 6MWD Changes from Baseline at Week 12 during Peak Plasma Concentration of Tyvaso

The placebo-corrected median treatment effect on 6MWD was estimated (using the Hodges-Lehmann estimator) within various subpopulations defined by age quartile, gender, geographic region of the study site, disease etiology, baseline 6MWD quartile, and type of background therapy (Figure 2).

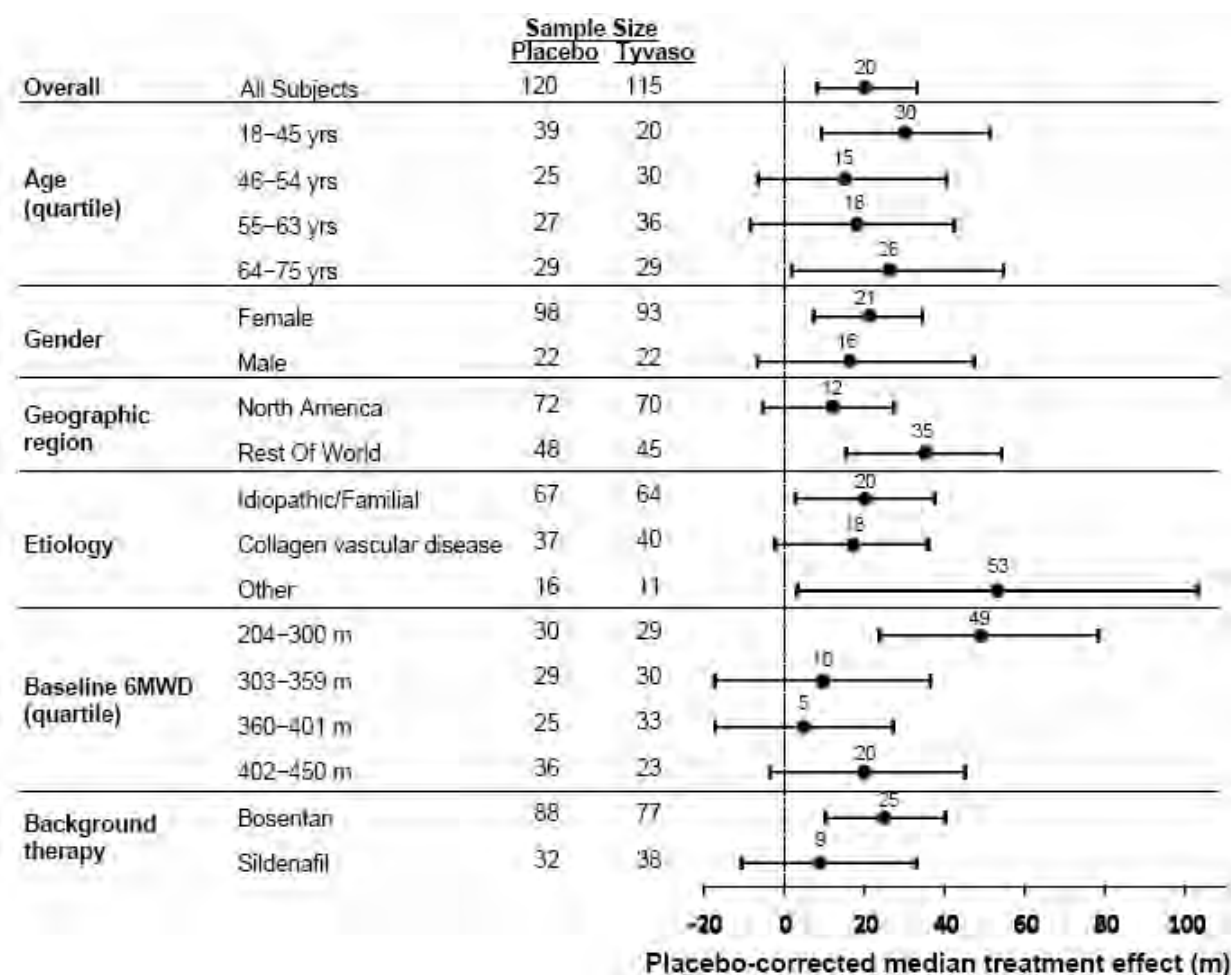


Figure 2. Placebo Corrected Median Treatment Effect (Hodges-Lehmann estimate with 95% CI) on 6MWD Change from Baseline at Week 12 During Peak Plasma Concentration of Tyvaso for Various Subgroups

16 HOW SUPPLIED/STORAGE AND HANDLING

Tyvaso (treprostinil) inhalation solution is supplied in 2.9 mL clear LDPE ampules packaged as four ampules in a foil pouch. Tyvaso is a clear colorless to slightly yellow solution containing 1.74 mg treprostinil per ampule at a concentration of 0.6 mg/mL.

Ampules of Tyvaso are stable until the date indicated when stored in the unopened foil pouch at 25°C (77°F), with excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Once the foil pack is opened, ampules should be used within 7 days. Because Tyvaso is light-sensitive, unopened ampules should be stored in the foil pouch.

One ampule of Tyvaso should be used each day in the Tyvaso Inhalation System. After a Tyvaso ampule is opened and transferred to the medicine cup, the solution should remain in the device for no more than one day (24 hours). Any remaining solution should be discarded at the end of the day.

Tyvaso Inhalation System Starter Kit containing 28 ampule carton of Tyvaso [seven foil pouches each containing four 2.9 mL ampules. Each ampule contains 1.74 mg treprostinil (0.6 mg per mL)] and the Tyvaso Inhalation System. (NDC 66302-206-01)

Tyvaso Inhalation System Refill Kit containing 28 ampule carton of Tyvaso [seven foil pouches each containing four 2.9 mL ampules. Each ampule contains 1.74 mg treprostinil (0.6 mg per mL)] and accessories. (NDC 66302-206-02)

2.9 mL LDPE ampule containing 1.74 mg treprostinil (0.6 mg per mL), carton containing 1 foil pouch with 4 ampules. (NDC 66302-206-03)

17 PATIENT COUNSELING INFORMATION

Patients should be properly trained in the administration process for Tyvaso, including dosing, Optineb-ir device set up, operation, cleaning, and maintenance, according to the instructions for use [*see Dosage and Administration (2.1)*].

To avoid potential interruptions in drug delivery because of equipment malfunction, patients should have access to a back-up Optineb-ir device [*see Dosage and Administration (2.4)*].

In the event that a scheduled treatment session is missed or interrupted, therapy should be resumed as soon as possible [*see Dosage and Administration (2.1)*].

Patients should avoid skin or eye contact with Tyvaso. If Tyvaso comes in contact with the skin or eyes, instruct patients to rinse immediately with water [*see Dosage and Administration (2.4)*].

US Patent No. 5,153,222
US Patent No. 6,765,117
US Patent No. 6,521,212
US Patent No. 6,756,033

United Therapeutics Corp.
Research Triangle Park, NC 27709

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Tyvaso manufactured by:

Catalent Pharma Solutions
Woodstock, IL 60098

For United Therapeutics Corp.
Research Triangle Park, NC 27709

July 2009

PATIENT PACKAGE INSERT

Tyvaso (Tī-vāsō)

(treprostinil)

Inhalation Solution

Read this Patient Package Insert before you start taking Tyvaso and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is Tyvaso?

Tyvaso is a prescription medicine used in adults to treat pulmonary arterial hypertension (PAH), which is high blood pressure in the arteries of your lungs. Tyvaso can improve the ability to do exercise in people who also take bosentan (an endothelin receptor antagonist (ERA)) or sildenafil (a phosphodiesterase-5 (PDE-5) inhibitor). Your ability to do exercise decreases 4 hours after taking Tyvaso.

It is not known if Tyvaso is safe or effective in people under 18 years of age.

What should I tell my healthcare provider before taking Tyvaso?

Before taking Tyvaso, tell your healthcare provider about all of your medical conditions, including if you:

- have lung disease, such as asthma or chronic obstructive pulmonary disease (COPD)
- have a lung infection
- have liver problems or kidney problems
- have low blood pressure
- are pregnant or plan to become pregnant. It is not known if Tyvaso will harm your unborn baby. Women who can become pregnant should use effective birth control while taking Tyvaso.
- are breast-feeding or plan to breast-feed. It is not known if Tyvaso passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby while taking Tyvaso.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Tyvaso and other medicines may affect each other.

Especially tell your healthcare provider if you take any of these medicines:

- medicines that decrease blood clotting
- water pills (diuretics)
- medicines used to treat high blood pressure or heart disease
- gemfibrozil (Lopid) (for high cholesterol)
- rifampin (Rimactane, Rifadin, Rifamate, Rifater) (for infection)

Know the medicines you take. Keep a list of them and show it to your healthcare provider and specialty pharmacist when you get a new medicine.

How should I take Tyvaso?

- Take Tyvaso each day exactly as your healthcare provider tells you.
- See the detailed Tyvaso Inhalation System Instructions for Use.
- Tyvaso is breathed in (inhaled) through your mouth into your lungs. Tyvaso should only be used with the Tyvaso Inhalation System.
- Tyvaso is taken in 4 treatment sessions each day during waking hours. The sessions should be at about 4 hours apart.
- At the beginning of each day, it will take about 5 minutes to prepare the Tyvaso Inhalation System. Each treatment session will take 2 to 3 minutes.
- Take your first Tyvaso treatment session in the morning and take your last treatment session before bedtime.
- Your healthcare provider may change your dose if needed.
- If you miss a dose of Tyvaso take it as soon as you remember.
- Do not let Tyvaso solution get into your eyes or onto your skin. If it does, rinse your skin or eyes right away with water.

What are the possible side effects of Tyvaso?

Tyvaso can cause serious side effects, including:

- Tyvaso may increase the risk of bleeding in people who take blood thinners (anticoagulants).
- If you have low blood pressure, Tyvaso may lower your blood pressure further.

Ask your healthcare provider if you are not sure if this applies to you.

The most common side effects of Tyvaso include:

- coughing
- headache
- nausea
- reddening of your face and neck (flushing)
- throat irritation and pain
- fainting or loss of consciousness

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of Tyvaso. For more information, ask your healthcare provider or specialty pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Tyvaso?

- Store Tyvaso ampules in the unopened foil pack between 59°F to 86°F (15°C to 30°C) until ready to use.
- When the foil pouch is opened, Tyvaso ampules should be used within 7 days.
- Tyvaso is sensitive to light. The unopened Tyvaso ampules should be stored in the foil pouch.
- After a Tyvaso ampule is opened and put into the medicine cup in the Tyvaso Inhalation System, Tyvaso can be kept in the medicine cup for no more than 1 day (24 hours).
- Tyvaso that is left in the medicine cup at the end of the day must be thrown away.

Keep Tyvaso and all medicines out of the reach of children.

General information about the safe and effective use of Tyvaso.

Medicines are sometimes prescribed for conditions that are not mentioned in a patient information leaflet. Do not use Tyvaso for a condition for which it was not prescribed. Do not give Tyvaso to other people, even if they have the same symptoms you have. It may harm them.

This patient information leaflet summarizes the most important information about Tyvaso. You can ask your healthcare provider or specialty pharmacist for information about Tyvaso that is written for health professionals.

For more information, go to www.tyvaso.com or call 1-866-458-6479.

What are the ingredients in Tyvaso?

Active ingredient: treprostinil

Inactive ingredients: sodium chloride, sodium citrate, sodium hydroxide, hydrochloric acid, and water for injection.

Tyvaso is a trademark of United Therapeutics Corporation.

Tyvaso is jointly marketed by United Therapeutics Corporation and Lung Rx, Inc.

Literature issued July 2009

United Therapeutics Corp.

Research Triangle Park, NC 27709 USA

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EXHIBIT 4

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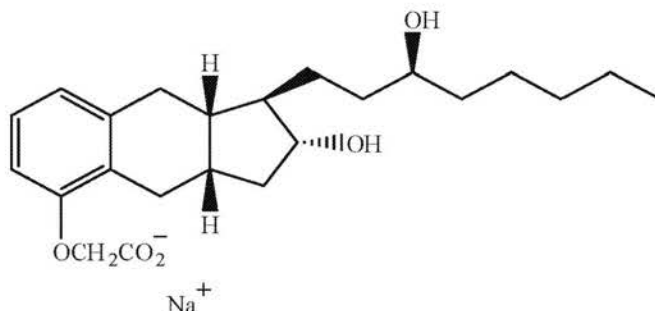
PRODUCT INFORMATION**REMODULIN® (Treprostinil sodium) Injection****DESCRIPTION**

Remodulin® (treprostinil sodium) Injection is a sterile sodium salt formulated for subcutaneous or intravenous administration. Remodulin is supplied in 20 mL multi-use vials in four strengths, containing 1 mg/mL, 2.5 mg/mL, 5 mg/mL or 10 mg/mL of treprostinil. Each mL also contains 5.3 mg sodium chloride (except for the 10 mg/mL strength which contains 4.0 mg sodium chloride), 3.0 mg metacresol, 6.3 mg sodium citrate, and water for injection. Sodium hydroxide and hydrochloric acid may be added to adjust pH between 6.0 and 7.2.

Treprostinil is chemically stable at room temperature and neutral pH.

Treprostinil sodium is (1R,2R,3aS,9aS)-[[2,3,3a,4,9,9a-Hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]acetic acid monosodium salt. Treprostinil sodium has a molecular weight of 412.49 and a molecular formula of $C_{23}H_{33}NaO_5$.

The structural formula of treprostinil sodium is:

**CLINICAL PHARMACOLOGY**

General: The major pharmacologic actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation. In animals, the vasodilatory effects reduce right and left ventricular afterload and increase cardiac output and stroke volume. Other studies have shown that treprostinil causes a dose-related negative inotropic and lusitropic effect. No major effects on cardiac conduction have been observed.

Pharmacokinetics

The pharmacokinetics of continuous subcutaneous Remodulin are linear over the dose range of 1.25 to 22.5 ng/kg/min (corresponding to plasma concentrations of about 0.03 to 8 mcg/L) and can be described by a two-compartment model. Dose proportionality at infusion rates greater than 22.5 ng/kg/min has not been studied.

Subcutaneous and intravenous administration of Remodulin demonstrated bioequivalence at steady state at a dose of 10 ng/kg/min.

Absorption: Remodulin is relatively rapidly and completely absorbed after subcutaneous infusion, with an absolute bioavailability approximating 100%. Steady-state concentrations occurred in approximately 10 hours. Concentrations in patients treated with an average dose of 9.3 ng/kg/min were approximately 2 mcg/L.

Distribution: The volume of distribution of the drug in the central compartment is approximately 14L/70 kg ideal body weight. Remodulin at *in vitro* concentrations ranging from 330-10,000 mcg/L was 91% bound to human plasma protein.

Metabolism: Remodulin is substantially metabolized by the liver, but the precise enzymes responsible are unknown. Five metabolites have been described (HU1 through HU5). The biological activity and metabolic fate of these metabolites are unknown. The chemical structure of HU1 is unknown. HU5 is the glucuronide conjugate of treprostinil. The other

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metabolites are formed by oxidation of the 3-hydroxyoctyl side chain (HU2) and subsequent additional oxidation (HU3) or dehydration (HU4). Based on the results of *in vitro* human hepatic cytochrome P450 studies, Remodulin does not inhibit CYP-1A2, 2C9, 2C19, 2D6, 2E1, or 3A. Whether Remodulin induces these enzymes has not been studied.

Excretion: The elimination of Remodulin is biphasic, with a terminal half-life of approximately 4 hours. Approximately 79% of an administered dose is excreted in the urine as unchanged drug (4%) and as the identified metabolites (64%). Approximately 13% of a dose is excreted in the feces. Systemic clearance is approximately 30 liters/hr for a 70 kg ideal body weight person.

Special Populations

Hepatic Insufficiency: In patients with portopulmonary hypertension and mild (n=4) or moderate (n=5) hepatic insufficiency, Remodulin at a subcutaneous dose of 10 ng/kg/min for 150 minutes had a C_{max} that was increased 2-fold and 4-fold, respectively, and an $AUC_{0-\infty}$ that was increased 3-fold and 5-fold, respectively, compared to healthy subjects. Clearance in patients with hepatic insufficiency was reduced by up to 80% compared to healthy adults.

In patients with mild or moderate hepatic insufficiency, the initial dose of Remodulin should be decreased to 0.625 ng/kg/min ideal body weight and should be increased cautiously. Remodulin has not been studied in patients with severe hepatic insufficiency.

Renal Insufficiency: No studies have been performed in patients with renal insufficiency, so no specific advice about dosing in such patients can be given. Although only 4% of the administered dose is excreted unchanged in the urine, the five identified metabolites are all excreted in the urine.

Effect of Other Drugs on Remodulin: *In vitro* studies: Remodulin did not significantly affect the plasma protein binding of normally observed concentrations of digoxin or warfarin.

In vivo studies: Acetaminophen - Analgesic doses of acetaminophen, 1000 mg every 6 hours for seven doses, did not affect the pharmacokinetics of Remodulin, at a subcutaneous infusion rate of 15 ng/kg/min.

Clinical Trials in Pulmonary Arterial Hypertension (PAH)

Two 12-week, multicenter, randomized, double-blind studies compared continuous subcutaneous infusion of Remodulin to placebo in a total of 470 patients with NYHA Class II-IV pulmonary arterial hypertension (PAH). PAH was primary in 58% of patients, associated with collagen vascular disease in 19%, and the result of congenital left to right shunts in 23%. The mean age was 45 (range 9 to 75 years). About 81% were female and 84% were Caucasian. Pulmonary hypertension had been diagnosed for a mean of 3.8 years. The primary endpoint of the studies was change in 6-minute walking distance, a standard measure of exercise capacity. There were many assessments of symptoms related to heart failure, but local discomfort and pain associated with Remodulin may have substantially unblinded those assessments. The 6-minute walking distance and an associated subjective measurement of shortness of breath during the walk (Borg dyspnea score) were administered by a person not participating in other aspects of the study. Remodulin was administered as a subcutaneous infusion, described in DOSAGE AND ADMINISTRATION, and the dose averaged 9.3 ng/kg/min at Week 12. Few subjects received doses > 40 ng/kg/min. Background therapy, determined by the investigators, could include anticoagulants, oral vasodilators, diuretics, digoxin, and oxygen but not an endothelin receptor antagonist or epoprostenol. The two studies were identical in design and conducted simultaneously, and the results were analyzed both pooled and individually.

Hemodynamic Effects

As shown in Table 1, chronic therapy with Remodulin resulted in small hemodynamic changes consistent with pulmonary and systemic vasodilation.

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Table 1: Hemodynamics During Chronic Administration of Remodulin in Patients with PAH

Hemodynamic Parameter	Baseline		Mean change from baseline at Week 12	
	Remodulin (N=204-231)	Placebo (N=215-235)	Remodulin (N=163-199)	Placebo (N=182-215)
CI (L/min/m ²)	2.4 ± 0.88	2.2 ± 0.74	+0.12 ± 0.58*	-0.06 ± 0.55
PAPm (mmHg)	62 ± 17.6	60 ± 14.8	-2.3 ± 7.3*	+0.7 ± 8.5
RAPm (mmHg)	10 ± 5.7	10 ± 5.9	-0.5 ± 5.0*	+1.4 ± 4.8
PVRI (mmHg/L/min/m ²)	26 ± 13	25 ± 13	-3.5 ± 8.2*	+1.2 ± 7.9
SVRI (mmHg/L/min/m ²)	38 ± 15	39 ± 15	-3.5 ± 12*	-0.80 ± 12
SvO ₂ (%)	62 ± 100	60 ± 11	+2.0 ± 10*	-1.4 ± 8.8
SAPm (mmHg)	90 ± 14	91 ± 14	-1.7 ± 12	-1.0 ± 13
HR (bpm)	82 ± 13	82 ± 15	-0.5 ± 11	-0.8 ± 11

*Denotes statistically significant difference between Remodulin and placebo, p<0.05.

CI = cardiac index; PAPm = mean pulmonary arterial pressure; PVRI = pulmonary vascular resistance indexed; RAPm = mean right atrial pressure; SAPm = mean systemic arterial pressure; SVRI = systemic vascular resistance indexed;

SvO₂ = mixed venous oxygen saturation; HR = heart rate.

Clinical Effects

The effect of Remodulin on 6-minute walk, the primary end point of the studies, was small and did not achieve conventional levels of statistical significance. For the combined populations, the median change from baseline on Remodulin was 10 meters and the median change from baseline on placebo was 0 meters. Although it was not the primary endpoint of the study, the Borg dyspnea score was significantly improved by Remodulin during the 6-minute walk, and Remodulin also had a significant effect, compared with placebo, on an assessment that combined walking distance with the Borg dyspnea score. Remodulin also consistently improved indices of dyspnea, fatigue and signs and symptoms of pulmonary hypertension, but these indices were difficult to interpret in the context of incomplete blinding to treatment assignment resulting from infusion site symptoms.

INDICATIONS AND USAGE

Remodulin® is indicated as a continuous subcutaneous infusion or intravenous infusion (for those not able to tolerate a subcutaneous infusion) for the treatment of pulmonary arterial hypertension in patients with NYHA Class II-IV symptoms (see **CLINICAL PHARMACOLOGY: Clinical Effects**) to diminish symptoms associated with exercise.

CONTRAINDICATIONS

Remodulin is contraindicated in patients with known hypersensitivity to the drug or to structurally related compounds.

WARNINGS

Remodulin is indicated for subcutaneous or intravenous use only.

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PRECAUTIONS**General**

Remodulin should be used only by clinicians experienced in the diagnosis and treatment of PAH.

Remodulin is a potent pulmonary and systemic vasodilator. Initiation of Remodulin must be performed in a setting with adequate personnel and equipment for physiological monitoring and emergency care. Therapy with Remodulin may be used for prolonged periods, and the patient's ability to administer Remodulin and care for an infusion system should be carefully considered.

Dose should be increased for lack of improvement in, or worsening of, symptoms and it should be decreased for excessive pharmacologic effects or for unacceptable infusion site symptoms (see **DOSAGE AND ADMINISTRATION**).

Abrupt withdrawal or sudden large reductions in dosage of Remodulin may result in worsening of PAH symptoms and should be avoided.

Information for Patients

Patients receiving Remodulin should be given the following information: Remodulin is infused continuously through a subcutaneous or surgically placed indwelling central venous catheter, via an infusion pump. Therapy with Remodulin will be needed for prolonged periods, possibly years, and the patient's ability to accept and care for a catheter and to use an infusion pump should be carefully considered. In order to reduce the risk of infection, aseptic technique must be used in the preparation and administration of Remodulin. Additionally, patients should be aware that subsequent disease management may require the initiation of an alternative intravenous prostacyclin therapy, Flolan® (epoprostenol sodium).

Drug Interactions

Reduction in blood pressure caused by Remodulin may be exacerbated by drugs that by themselves alter blood pressure, such as diuretics, antihypertensive agents, or vasodilators. Since Remodulin inhibits platelet aggregation, there is also a potential for increased risk of bleeding, particularly among patients maintained on anticoagulants. During clinical trials, Remodulin was used concurrently with anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, analgesics, antipyretics, nonsteroidal anti-inflammatories, opioids, corticosteroids, and other medications.

Remodulin has not been studied in conjunction with Flolan or Tracleer® (bosentan).

Effect of Other Drugs on Remodulin

In vivo studies: Acetaminophen - Analgesic doses of acetaminophen, 1000 mg every 6 hours for seven doses, did not affect the pharmacokinetics of Remodulin, at a subcutaneous infusion rate of 15 ng/kg/min.

Effect of Remodulin on Other Drugs

In vitro studies: Remodulin did not significantly affect the plasma protein binding of normally observed concentrations of digoxin or warfarin.

In vivo studies: Warfarin - Remodulin does not affect the pharmacokinetics or pharmacodynamics of warfarin. The pharmacokinetics of R- and S- warfarin and the INR in healthy subjects given a single 25 mg dose of warfarin were unaffected by continuous subcutaneous Remodulin at an infusion rate of 10 ng/kg/min.

Hepatic and Renal Impairment

Caution should be used in patients with hepatic or renal impairment (see **Special Populations**).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies have not been performed to evaluate the carcinogenic potential of treprostinil. *In vitro* and *in vivo* genetic toxicology studies did not demonstrate any mutagenic or clastogenic effects of treprostinil. Treprostinil sodium did not affect fertility or mating performance of male or female rats given continuous subcutaneous infusions at rates of up to 450 ng treprostinil/kg/min [about 59 times the recommended starting human rate of infusion (1.25 ng/kg/min) and about 8 times the average rate (9.3 ng/kg/min) achieved in clinical trials, on a ng/m² basis]. In this study, males were dosed from 10 weeks prior to mating and through the 2-week mating period. Females were dosed from 2 weeks prior to mating until gestational day 6.

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Pregnancy

Pregnancy Category B - In pregnant rats, continuous subcutaneous infusions of treprostinil sodium during organogenesis and late gestational development, at rates as high as 900 ng treprostinil/kg/min (about 117 times the starting human rate of infusion, on a ng/m² basis and about 16 times the average rate achieved in clinical trials), resulted in no evidence of harm to the fetus. In pregnant rabbits, effects of continuous subcutaneous infusions of treprostinil during organogenesis were limited to an increased incidence of fetal skeletal variations (bilateral full rib or right rudimentary rib on lumbar 1) associated with maternal toxicity (reduction in body weight and food consumption) at an infusion rate of 150 ng treprostinil/kg/min (about 41 times the starting human rate of infusion, on a ng/m² basis, and 5 times the average rate used in clinical trials). In rats, continuous subcutaneous infusion of treprostinil from implantation to the end of lactation, at rates of up to 450 ng treprostinil/kg/min, did not affect the growth and development of offspring. Because animal reproduction studies are not always predictive of human response, Remodulin should be used during pregnancy only if clearly needed.

Labor and delivery

No treprostinil sodium treatment-related effects on labor and delivery were seen in animal studies. The effect of treprostinil sodium on labor and delivery in humans is unknown.

Nursing mothers

It is not known whether treprostinil is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, caution should be exercised when Remodulin is administered to nursing women.

Pediatric use

Safety and effectiveness in pediatric patients have not been established. Clinical studies of Remodulin did not include sufficient numbers of patients aged ≤16 years to determine whether they respond differently from older patients. In general, dose selection should be cautious.

Geriatric use

Clinical studies of Remodulin did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Patients receiving Remodulin as a subcutaneous infusion reported a wide range of adverse events, many potentially related to the underlying disease (dyspnea, fatigue, chest pain, right ventricular heart failure, and pallor). During clinical trials with subcutaneous infusion of Remodulin, infusion site pain and reaction were the most common adverse events among those treated with Remodulin. Infusion site reaction was defined as any local adverse event other than pain or bleeding/bruising at the infusion site and included symptoms such as erythema, induration or rash. Infusion site reactions were sometimes severe and could lead to discontinuation of treatment.

Table 2. Percentages of subjects reporting subcutaneous infusion site adverse events

	Reaction		Pain	
	Placebo	Remodulin	Placebo	Remodulin
Severe	1	38	2	39
Requiring narcotics*	NA**	NA**	1	32
Leading to discontinuation	0	3	0	7

* based on prescriptions for narcotics, not actual use

**medications used to treat infusion site pain were not distinguished from those used to treat site reactions

Other adverse events included diarrhea, jaw pain, edema, vasodilatation and nausea, and these are generally considered to be related to the pharmacologic effects of Remodulin, whether administered subcutaneously or intravenously.

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Adverse Events During Chronic Dosing

Table 3 lists adverse events that occurred at a rate of at least 3% and were more frequent in patients treated with subcutaneous Remodulin than with placebo in controlled trials in PAH.

Table 3: Adverse Events in Controlled Studies of Patients with PAH, Occurring with at Least 3% Incidence and More Common on Subcutaneous Remodulin than on Placebo.

Adverse Event	Remodulin (N=236) Percent of Patients	Placebo (N=233) Percent of Patients
Infusion Site Pain	85	27
Infusion Site Reaction	83	27
Headache	27	23
Diarrhea	25	16
Nausea	22	18
Rash	14	11
Jaw Pain	13	5
Vasodilatation	11	5
Dizziness	9	8
Edema	9	3
Pruritus	8	6
Hypotension	4	2

Reported adverse events (at least 3%) are included except those too general to be informative, and those not plausibly attributable to the use of the drug, because they were associated with the condition being treated or are very common in the treated population.

Adverse Events Attributable to the Drug Delivery System

In controlled studies of Remodulin administered subcutaneously, there were no reports of infection related to the drug delivery system. There were 187 infusion system complications reported in 28% of patients (23% Remodulin, 33% placebo); 173 (93%) were pump related and 14 (7%) related to the infusion set. Eight of these patients (4 Remodulin, 4 Placebo) reported non-serious adverse events resulting from infusion system complications. Adverse events resulting from problems with the delivery systems were typically related to either symptoms of excess Remodulin (e.g., nausea) or return of PAH symptoms (e.g., dyspnea). These events were generally resolved by correcting the delivery system pump or infusion set problem such as replacing the syringe or battery, reprogramming the pump, straightening a crimped infusion line. Adverse events resulting from problems with the delivery system did not lead to clinical instability or rapid deterioration.

There are no controlled clinical studies with Remodulin administered intravenously. Among the subjects (n=38) treated for 12-weeks in an open-label study, 2 patients had either line infections or sepsis. Other events potentially related to the mode of infusion include arm swelling, paresthesias, hematoma and pain.

OVERDOSAGE

Signs and symptoms of overdose with Remodulin during clinical trials are extensions of its dose-limiting pharmacologic effects and include flushing, headache, hypotension, nausea, vomiting, and diarrhea. Most events were self-limiting and resolved with reduction or withholding of Remodulin.

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In controlled clinical trials, seven patients received some level of overdose and in open-label follow-on treatment seven additional patients received an overdose; these occurrences resulted from accidental bolus administration of Remodulin, errors in pump programmed rate of administration, and prescription of an incorrect dose. In only two cases did excess delivery of Remodulin produce an event of substantial hemodynamic concern (hypotension, near-syncope).

DOSAGE AND ADMINISTRATION

Remodulin® is supplied in 20 mL vials in concentrations of 1 mg/mL, 2.5 mg/mL, 5 mg/mL and 10 mg/mL. Remodulin can be administered as supplied or diluted for intravenous infusion with Sterile Water for Injection or 0.9% Sodium Chloride Injection prior to administration.

Initial Dose

Remodulin is administered by continuous infusion. Remodulin is preferably infused subcutaneously, but can be administered by a central intravenous line if the subcutaneous route is not tolerated, because of severe site pain or reaction. The infusion rate is initiated at 1.25 ng/kg/min. If this initial dose cannot be tolerated because of systemic effects, the infusion rate should be reduced to 0.625 ng/kg/min.

Dosage Adjustments

The goal of chronic dosage adjustments is to establish a dose at which PAH symptoms are improved, while minimizing excessive pharmacologic effects of Remodulin (headache, nausea, emesis, restlessness, anxiety and infusion site pain or reaction).

The infusion rate should be increased in increments of no more than 1.25 ng/kg/min per week for the first four weeks and then no more than 2.5 ng/kg/min per week for the remaining duration of infusion, depending on clinical response. There is little experience with doses >40 ng/kg/min. Abrupt cessation of infusion should be avoided (see **PRECAUTIONS**).

Administration

Subcutaneous Infusion

Remodulin is administered subcutaneously by continuous infusion, via a self-inserted subcutaneous catheter, using an infusion pump designed for subcutaneous drug delivery. To avoid potential interruptions in drug delivery, the patient must have immediate access to a backup infusion pump and subcutaneous infusion sets. The ambulatory infusion pump used to administer Remodulin should: (1) be small and lightweight, (2) be adjustable to approximately 0.002 mL/hr, (3) have occlusion/no delivery, low battery, programming error and motor malfunction alarms, (4) have delivery accuracy of $\pm 6\%$ or better and (5) be positive pressure driven. The reservoir should be made of polyvinyl chloride, polypropylene or glass.

For subcutaneous infusion, Remodulin is **delivered without further dilution** at a calculated Subcutaneous Infusion Rate (mL/hr) based on a patient's Dose (ng/kg/min), Weight (kg), and the Vial Strength (mg/mL) of Remodulin being used. During use, a single reservoir (syringe) of undiluted Remodulin can be administered up to 72 hours at 37°C. The Subcutaneous Infusion rate is calculated using the following formula:

$$\text{Subcutaneous Infusion Rate (mL/hr)} = \frac{\text{Dose (ng/kg/min)} \times \text{Weight (kg)} \times 0.00006^*}{\text{Remodulin Vial Strength (mg/mL)}}$$

*Conversion factor of 0.00006 = 60 min/hour x 0.000001 mg/ng

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Example calculations for *Subcutaneous Infusion* are as follows:

Example 1:

For a 60 kg person at the recommended initial dose of 1.25 ng/kg/min using the 1 mg/mL Remodulin Vial Strength, the infusion rate would be calculated as follows:

$$\begin{array}{l} \text{Subcutaneous} \\ \text{Infusion Rate} \\ \text{(mL/hr)} \end{array} = \frac{1.25 \text{ ng/kg/min} \times 60 \text{ kg} \times 0.00006}{1 \text{ mg/mL}} = 0.005 \text{ mL/hr}$$

Example 2:

For a 65 kg person at a dose of 40 ng/kg/min using the 5 mg/mL Remodulin Vial Strength, the infusion rate would be calculated as follows:

$$\begin{array}{l} \text{Subcutaneous} \\ \text{Infusion Rate} \\ \text{(mL/hr)} \end{array} = \frac{40 \text{ ng/kg/min} \times 65 \text{ kg} \times 0.00006}{5 \text{ mg/mL}} = 0.031 \text{ mL/hr}$$

Intravenous Infusion

Remodulin must be diluted with either Sterile Water for Injection or 0.9% Sodium Chloride Injection and is administered intravenously by continuous infusion, via a surgically placed indwelling central venous catheter, using an infusion pump designed for intravenous drug delivery. To avoid potential interruptions in drug delivery, the patient must have immediate access to a backup infusion pump and infusion sets. The ambulatory infusion pump used to administer Remodulin should: (1) be small and lightweight, (2) have occlusion/no delivery, low battery, programming error and motor malfunction alarms, (3) have delivery accuracy of $\pm 6\%$ or better of the hourly dose, and (4) be positive pressure driven. The reservoir should be made of polyvinyl chloride, polypropylene or glass.

Diluted Remodulin has been shown to be stable at ambient temperature for up to 48 hours at concentrations as low as 0.004 mg/mL (4,000 ng/mL).

When using an appropriate infusion pump and reservoir, a predetermined intravenous infusion rate should first be selected to allow for a desired infusion period length of up to 48 hours between system changeovers. Typical intravenous infusion system reservoirs have volumes of 50 or 100 mL. With this selected Intravenous Infusion Rate (mL/hr) and the patient's Dose (ng/kg/min) and Weight (kg), the Diluted Intravenous Remodulin Concentration (mg/mL) can be calculated using the following formula:

$$\begin{array}{l} \text{Step 1} \\ \text{Diluted} \\ \text{Intravenous} \\ \text{Remodulin} \\ \text{Concentration} \\ \text{(mg/mL)} \end{array} = \frac{\text{Dose} \text{ (ng/kg/min)} \times \text{Weight} \text{ (kg)} \times 0.00006}{\text{Intravenous Infusion Rate} \text{ (mL/hr)}}$$

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The Amount of Remodulin Injection needed to make the required Diluted Intravenous Remodulin Concentration for the given reservoir size can then be calculated using the following formula:

Step 2 Amount of Remodulin Injection (mL)	=	Diluted Intravenous Remodulin Concentration (mg/mL)	x	Total Volume of Diluted Remodulin Solution in Reservoir (mL)
		Remodulin Vial Strength (mg/mL)		

The calculated amount of Remodulin Injection is then added to the reservoir along with the sufficient volume of diluent (Sterile Water for Injection or 0.9% Sodium Chloride Injection) to achieve the desired total volume in the reservoir.

Example calculations for *Intravenous Infusion* are as follows:

Example 3:

For a 60 kg person at a dose of 5 ng/kg/min, with a predetermined intravenous infusion rate of 1 mL/hr and a reservoir of 50 mL, the Diluted Intravenous Remodulin Solution Concentration would be calculated as follows:

$$\begin{array}{l} \text{Step 1} \\ \text{Diluted} \\ \text{Intravenous} \\ \text{Remodulin} \\ \text{Concentration} \\ \text{(mg/mL)} \end{array} = \frac{5 \text{ ng/kg/min} \times 60 \text{ kg} \times 0.00006}{1 \text{ mL/hr}} = 0.018 \text{ mg/mL} \quad (18,000 \text{ ng/mL})$$

The Amount of Remodulin Injection (using 1 mg/mL Vial Strength) needed for a total Diluted Remodulin Concentration of 0.018 mg/mL and a total volume of 50 mL would be calculated as follows:

Step 2 Amount of Remodulin Injection (mL)	=	0.018 mg/mL	x 50 mL = 0.9 mL
		1 mg/mL	

The Diluted Intravenous Remodulin Concentration for the person in Example 3 would thus be prepared by adding 0.9 mL of 1 mg/mL Remodulin Injection to a suitable reservoir along with a sufficient volume of diluent to achieve a total volume of 50 mL in the reservoir. The pump flow rate for this example would be set at 1 mL/hr.

Example 4:

For a 75 kg person at a dose of 30 ng/kg/min, with a predetermined intravenous infusion rate of 2 mL/hr, and a reservoir of 100 mL, the Diluted Intravenous Remodulin Solution Concentration would be calculated as follows:

$$\begin{array}{l} \text{Step 1} \\ \text{Diluted} \\ \text{Intravenous} \\ \text{Remodulin} \\ \text{Concentration} \\ \text{(mg/mL)} \end{array} = \frac{30 \text{ ng/kg/min} \times 75 \text{ kg} \times \frac{0.00006}{6}}{2 \text{ mL/hr}} = 0.0675 \text{ mg/mL} \quad (67,500 \text{ ng/mL})$$

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The Amount of Remodulin Injection (using 2.5 mg/mL Vial Strength) needed for a total Diluted Remodulin Concentration of 0.0675 mg/mL and a total volume of 100 mL would be calculated as follows:

Step 2 Amount of Remodulin Injection (mL)	=	0.0675 mg/mL	x 100 mL = 2.7 mL
		2.5 mg/mL	

The Diluted Intravenous Remodulin Concentration for the person in Example 4 would thus be prepared by adding 2.7 mL of 2.5 mg/mL Remodulin Injection to a suitable reservoir along with a sufficient volume of diluent to achieve a total volume of 100 mL in the reservoir. The pump flow rate for this example would be set at 2 mL/hr.

HOW SUPPLIED

Remodulin® is supplied in 20 mL multi-use vials at concentrations of 1mg/mL, 2.5 mg/mL, 5 mg/mL, and 10 mg/mL treprostinil, as sterile solutions in water for injection, individually packaged in a carton. Each mL contains treprostinil sodium equivalent to 1mg/mL, 2.5 mg/mL, 5 mg/mL, or 10 mg/mL treprostinil. Unopened vials of Remodulin are stable until the date indicated when stored at 15 to 25°C

(59 to 77°F). Store at 25°C (77°F), with excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

During use, a single reservoir (syringe) of undiluted Remodulin can be administered up to 72 hours at 37°C. Diluted Remodulin Solution can be administered up to 48 hours at 37°C when diluted to concentrations as low as 0.004 mg/mL in Sterile Water for Injection or 0.9% Sodium Chloride Injection. A single vial of Remodulin should be used for no more than 30 days after the initial introduction into the vial.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. If either particulate matter or discoloration is noted, Remodulin should not be administered.

20-mL vial containing treprostinil sodium equivalent to 1 mg treprostinil per mL, carton of 1 (NDC 66302-101-01).

20-mL vial containing treprostinil sodium equivalent to 2.5 mg treprostinil per mL, carton of 1 (NDC 66302-102-01).

20-mL vial containing treprostinil sodium equivalent to 5 mg treprostinil per mL, carton of 1 (NDC 66302-105-01).

20-mL vial containing treprostinil sodium equivalent to 10mg treprostinil per mL, carton of 1 (NDC 66302-110-01).

US Patent No. 5,153,222 (Use Patent)

United Therapeutics Corp.
Research Triangle Park, NC 27709

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REMODULIN manufactured by:

Baxter Pharmaceutical Solutions LLC
Bloomington, IN 47403

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For United Therapeutics Corp.
Research Triangle Park, NC 27709

Rx only

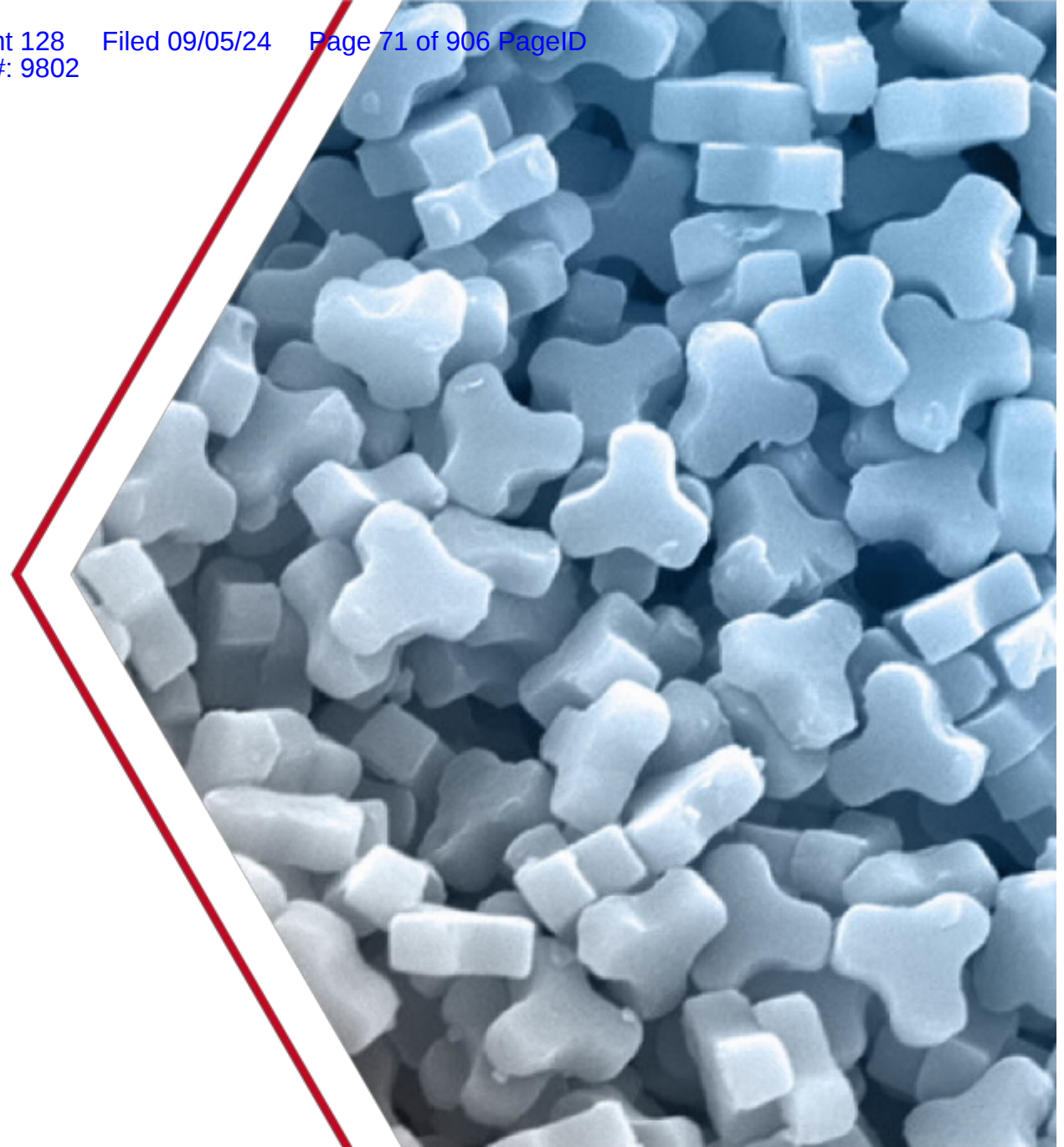
November 2004

EXHIBIT 5



Corporate Overview

June 20, 2022



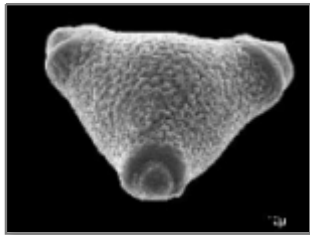
Engineered Particles to Enhance Delivery to Lower Lung

Monodisperse Particles with Precise Geometries for Inhalation

Shape influences aerodynamic performance

Inspired by nature

Pollen Particle



Eperua schomburgkiana

**YUTREPIA
PRINT particles**

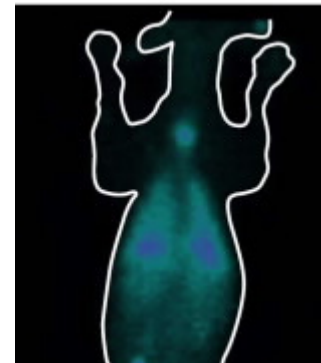


- 1.3 μm MMAD
- Trefoil shape

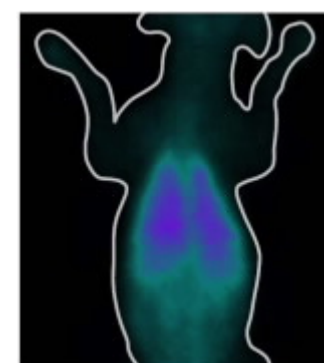
Size influences alveolar deposition

Particle sizes $\leq 5 \mu\text{m}$ are respirable but deposit differently

**4.6 μm MMAD
particle**



**1.3 μm MMAD
particle**



Tc⁹⁹ scintigraphy of PRINT particles in canine model¹



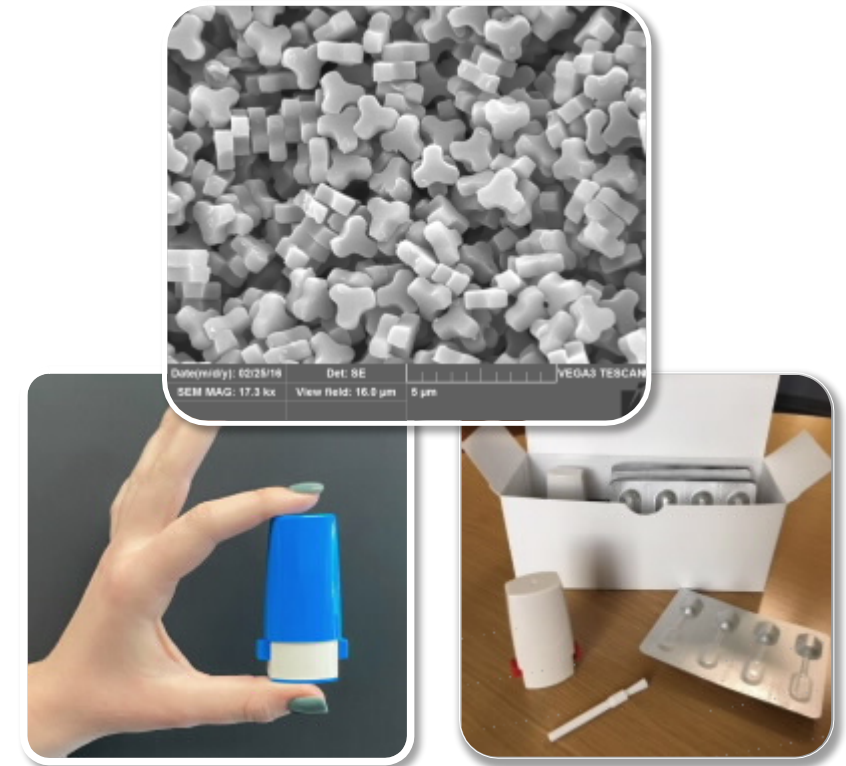
Provides preferential delivery to alveolar region and less upper airway deposition

YUTREPIA™ (treprostinil) inhalation powder

Engineered to enhance delivery to lower lung of PAH patients

FDA Tentative Approval on November 8, 2021¹

- **Approved based on safety data from INSPIRE trial (n=121)**
- **Demonstrated comparable bioavailability of 9 breaths Tyvaso® with only 2 breaths from a single capsule**
- **Administered doses comparable to 24 breaths of Tyvaso® 4x daily**
- **No Maximum Tolerated Dose identified**
- **IP position protected with patent claims into 2037**
 - Includes claims that cover the use of ~100 to 300mcg dry-power treprostinil to treat pulmonary hypertension²
- **Potential commercial launch subject to ongoing IP litigation with UTHR**



1. Pulmonary Hypertension (PH), 1. [Nov 8, 2021 press release](#); 2. [Aug 28, 2020 press release](#); Tyvaso® is a registered trademarks of United Therapeutics Corporation (UTHR)

YUTREPIA™ Checks All the Boxes for a Preferred Product Profile

We believe YUTREPIA is positioned to become the prostacyclin of first-choice

Portability	Replace burden of nebulizers with palm-sized, simple device; potential for earlier use
Tolerability	Reduce systemic toxicity when adding prostacyclin to naïve patients or escalating dose
Titratibility	Demonstrate safe titration to doses comparable to 24 breaths Tyvaso, 4x day
Durability	Potential to treat patients longer before transitioning to more invasive parenteral forms
Storage	Store at room temperature for product lifetime
Device Resistance	Accommodate wide range of lung capacities by using low resistance device
Device Position	Avoid product spillage by using capsule-based drug and trusted device

YUTREPIA™
✓
✓
✓
✓
✓
✓
✓

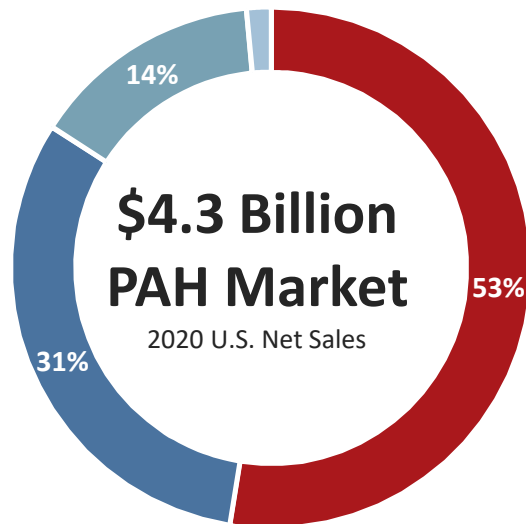
Tyvaso® is a registered trademarks of United Therapeutics Corporation (UTHR)

YUTREPIA Has Potential to Rapidly Garner Significant Market Share

Goal of prostanoid therapy is to dose to highest tolerable level to provide symptomatic benefit

■ Prostanoid ■ ERA ■ sGC ■ PDE5

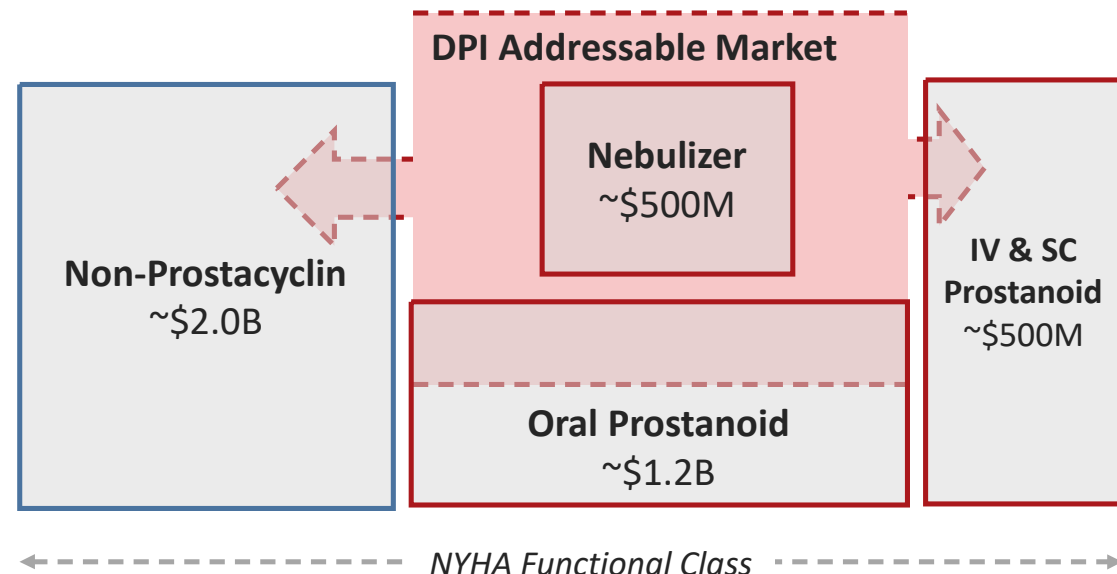
Analogs & IPa



>50% of prostanoid market included treprostinil formulations (\$1.2 billion)

Expect paradigm shift in treatment as DPIs grow inhaled market in PAH






- + Fewer systemic toxicities with targeted lower lung delivery
- + Portability, Tolerability, Titratability, Durability
- + Cannibalize nebulizers, capture oral share, earlier use, & delay parenteral



U.S. sales sourced from 2020 10-K SEC filings from United Therapeutics, JNJ, Gilead, Bayer, Merck; New York Heart Association (NYHA)

WHO Group 1 Represents a Significant Initial Market Opportunity

Additional WHO Groups Provide Market Expansion Opportunities

Pulmonary Hypertension	WHO Group 1 Due to PAH	PAH ~45,000 patients 2 local options (nebulized)	Oral	 orenitram treprostinil <small>orally administered</small>	 Uptravi saxipag	Tentative FDA approval YUTREPIA™ Potential 1st line prostacyclin in PAH
	WHO Group 2 Due to Left Heart Disease		IV/SC	 REMODYLIN treprostinil Injection	epoprostenol	
	WHO Group 3 Due to Chronic Lung Disease	PH-ILD ~30,000 patients Only 1 approved Rx	Nebulized	 TYVASO treprostinil nebulizer solution	 Ventavis treprostinil nebulizer solution	
	WHO Group 4 Due to CTEPH		PH-COPD <ul style="list-style-type: none">~100,000 pts with No Approved Treatments1 nebulized pivotal trial on-going²			Potential future indications for YUTREPIA
	WHO Group 5 Due to unclear MOA		For PH-ILD (FDA 2021) ¹			
Not PH	IPF Idiopathic Pulmonary Fibrosis	IPF <ul style="list-style-type: none">~100,000 pts with No Inhaled Treatments1 nebulized pivotal trial on-going³				Potential future indications for YUTREPIA

Pulmonary Arterial Hypertension (PAH); Pulmonary Hypertension (PH); Interstitial Lung Disease (ILD); Chronic Obstructive Pulmonary Disorder (COPD); Idiopathic Pulmonary Fibrosis (IPF); Patient estimates sourced by combination of Liquidia internal estimate and public statements by United Therapeutics (Feb 2022);

1. <https://www.nejm.org/doi/full/10.1056/NEJMoa2008470>; 2. <https://clinicaltrials.gov/ct2/show/NCT03496623>; 3. <https://www.clinicaltrials.gov/ct2/show/NCT04708782>

Deep Experience Within PAH, Rare Disease and Inhaled Products



Roger Jeffs
Chief Executive Officer

- Former UTHR Executive (18 yrs) including President/COO (2001-14) & co-CEO (2015-16)
- Led R&D, secured FDA approval of 6 rare diseases products at United Therapeutics



Rajeev Saggar, M.D.
Chief Medical Officer

- 20+ yrs practicing pulmonologist with 60+ peer-reviewed publications incl. PAH & PH-ILD
- Served as Interim Chief of Div. of Pulmonary Critical Care at Univ. of Arizona, College of Medicine; Medical Director of PH & Fibrosis Pgms and Lung Transplant at Banner University Medical Center

Announced Jun 20th
with July 18, 2022 start



Scott Moomaw
Senior VP Commercial

- Former UTHR VP Marketing (5 yrs) responsible for Remodulin®, Tyvaso® & Orenitram®
- Co-founded RareGen as COO (2018) launching generic Treprostinil Injection



Matt Snow
Vice President National Sales

- Former UTHR commercial leader (7 yrs) in multiple roles in sales leadership and training
- Launched rare disease products for SOBI (National Sales Dir.) & INSMED (Regional Lead)

Existing Commercial Presence in PAH with Treprostinil Injection

Specialty field sales team & co-pay programs replicate experience with branded drug



- ✓ Equivalent product
- ✓ Reliable Supply
- ✓ Seamless Service
- ✓ Lower Price

- 400+ unique prescribers switched patients from brand to generic
- More than doubled active patients after SC route added (Apr'21)
- ~500 active treprostinil injections patients in 1Q2022
- Planning for growth as payer generic mandates enforced
- Additional larger payers plan to implement mandates in 2022



Thank You

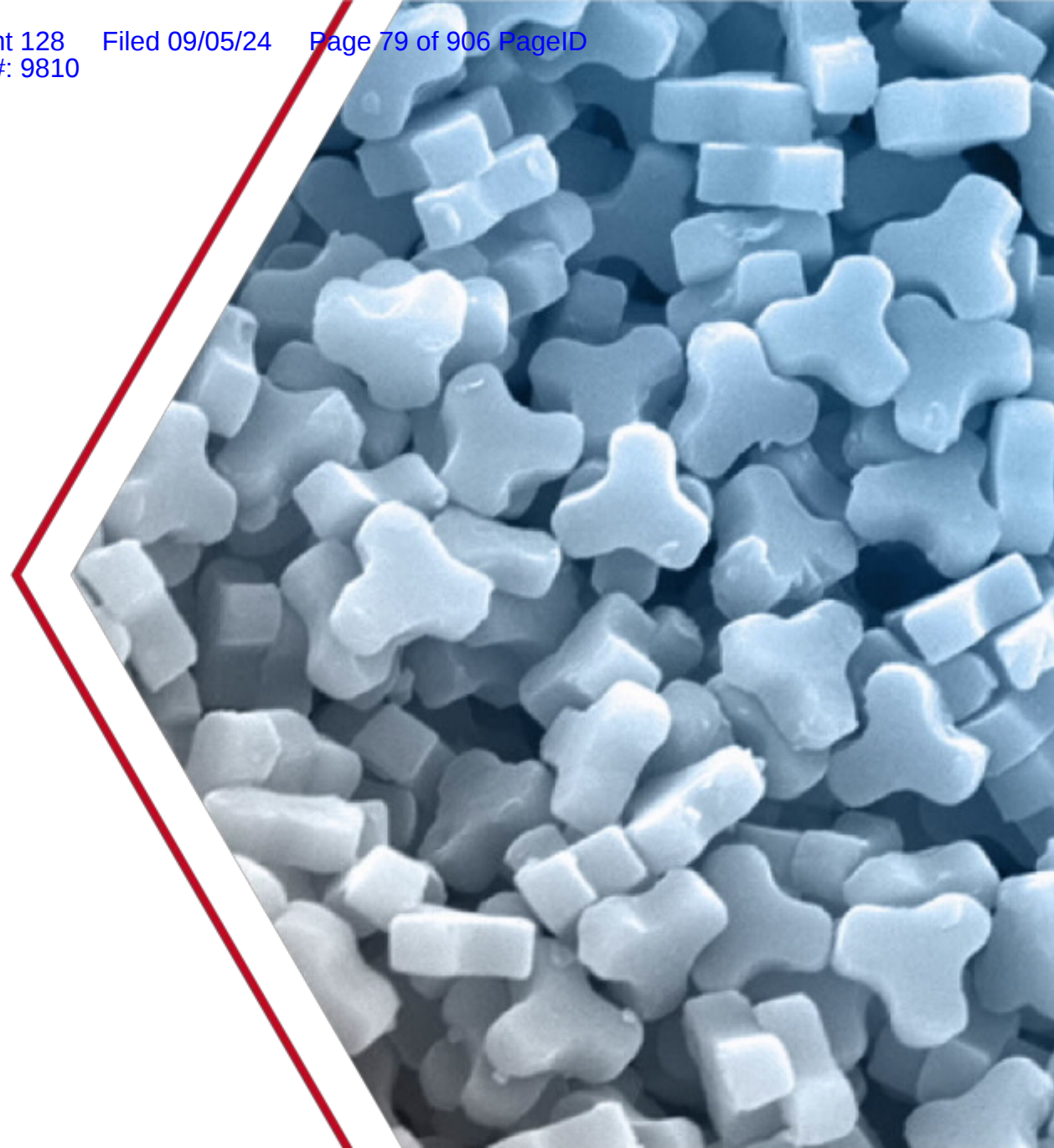


EXHIBIT 6

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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

(Mark One)

☒ ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended December 31, 2018

or

☐ TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the transition period from

to

Commission File Number: 001-38601

LIQUIDIA TECHNOLOGIES, INC.

(Exact Name of Registrant as Specified in Its Charter)

Delaware

(State or Other Jurisdiction of Incorporation or Organization)

20-1926605

(I.R.S. Employer Identification No.)

**419 Davis Drive, Suite 100
Morrisville, North Carolina**

(Address of Principal Executive Offices)

27560

(Zip Code)

Registrant's telephone number, including area code: **(919) 328-4400**

Securities registered pursuant to Section 12(b) of the Act:

Title of each class

Common stock, par value \$0.001 per share

Name of each exchange on which registered

NASDAQ Stock Market LLC

Securities registered pursuant to Section 12(g) of the Act: **None**

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☐ No ☒

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☒

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company" and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large Accelerated Filer ☐

Accelerated Filer ☐

Non-accelerated Filer ☒

Smaller Reporting Company ☒

Emerging Growth Company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act ☒

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☒

The registrant was not a public company as of the last business day of its most recently completed second fiscal quarter (June 30, 2018) so a calculation of the aggregate market value of the voting and non-voting common stock held by non-affiliates of the registrant at such time is not possible.

As of February 22, 2019, there were 15,563,641 shares of the issuer's common stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Liquidia Technologies, Inc. definitive proxy statement to be filed pursuant to Regulation 14A within 120 days after the end of the fiscal year are incorporated by reference into Part III of this annual report on Form 10-K and certain documents are incorporated by reference into Part IV.

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This annual report on Form 10-K includes our trademarks, trade names and service marks, such as Liquidia, the Liquidia logo and PRINT, or Particle Replication In Non-wetting Templates, which are protected under applicable intellectual property laws and are the property of Liquidia Technologies, Inc. This annual report also contains trademarks, trade names and service marks of other companies, which are the property of their respective owners. Solely for convenience,

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trademarks, trade names and service marks referred to in this annual report may appear without the ®, ™ or SM symbols, but such references are not intended to indicate, in any way, that we will not assert, to the fullest extent under applicable law, our rights or the right of the applicable licensor to these trademarks, trade names and service marks. We do not intend our use or display of other parties' trademarks, trade names or service marks to imply, and such use or display should not be construed to imply, a relationship with, or endorsement or sponsorship of us by, these other parties.

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the United States by establishing targeted sales and marketing teams. After reviewing the results of all of our Phase 2-enabling toxicology studies for LIQ865, and subject to the availability of sufficient funding, we will develop and commercialize LIQ865 independently, if it is ultimately approved, or seek to license this product candidate to one or more third parties. Outside of the United States, we intend to pursue the regulatory approval and commercialization of LIQ861 and LIQ865 with pharmaceutical companies with regional expertise.

- **Expand our internal pipeline leveraging our PRINT technology.** We intend to continue targeting diseases where we believe our PRINT technology can improve the efficacy, safety and patient experience of current treatments that have been impaired by suboptimal drug product formulation and delivery. We plan to focus initially on the development of improved and differentiated drug products containing FDA-approved APIs with proven efficacy and safety profiles eligible to use the 505(b)(2) regulatory pathway. In addition, we may expand our clinical development of LIQ861 and LIQ865, where appropriate, into broader indications or new applications.
- **Pursue strategic collaborations to maximize the value of products enabled by PRINT technology.** In addition to advancing our own internal product candidates, we have collaborated, and may consider collaborating, with pharmaceutical companies to develop their own product candidates across a wide range of therapeutic areas, molecule types and routes of administration, leveraging our PRINT technology. We believe that collaborating with pharmaceutical companies helps advance new PRINT capabilities, while adding to our intellectual property portfolio.

Our Competitive Strengths

We believe that we have several key strengths that have contributed to the development of our business and that will help us to realize our goal of becoming a biopharmaceutical company across research, development and commercialization activities. Our competitive strengths include:

- ***Our PRINT technology gives us the capability to overcome the constraints of conventional formulation and production methods and can be applied broadly across therapeutic areas, molecule types and routes of administration.*** Our PRINT technology allows us to precisely engineer drug particles in a wide variety of compositions, sizes and shapes and achieve a high level of control over the physical and chemical characteristics of drug particles, as compared to conventional formulation and production methods. PRINT particles can be designed to address specific pharmacological or therapeutic objectives, such as enhancing the route of administration, improving solubility, enhancing stability or extending therapeutic effects. Using our PRINT technology, we are able to engineer, among others, small molecule and biologic particles, single agent drug and combination drug particles and vaccine particles to improve efficacy, safety and convenience for patients. Our internal pipeline strategy is currently focused on developing proprietary innovations to currently approved drug products in order to minimize development risks and increase speed to market. In particular, we have designed LIQ861 to maximize the therapeutic benefits of treprostinil in treating PAH by safely delivering higher doses into the lungs using a convenient, palm-sized, disposable DPI. We believe that this may lead to a more attractive product profile with a more convenient method of administering the drug, as compared to the existing inhaled therapies that are currently available. We have also designed LIQ865 with the intention of providing patients with local post-operative analgesia for three to five days. We believe this would provide a longer period of pain relief than the existing local-acting pain drugs that are available, which could be a positive feature in light of interest in reducing the patient's reliance on opioids and non-steroidal anti-inflammatory drugs, or NSAIDs, for local post-operative pain management.

Our PRINT technology is broadly applicable — across therapeutic areas, molecule types and routes of administration — providing us with opportunities for future drug product development.

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- ***We have scaled operations with rapid and cost-effective transition to clinical development and commercial production.*** We believe our research and development operations and PRINT technology allow us to transition rapidly and cost-effectively from laboratory to clinical development and ultimately commercial-scale manufacture of drug particles. Utilizing well-established techniques from other roll-to-roll manufacturing processes, we have scaled PRINT technology to support the quality and quantity needs for clinical and, we believe, commercial production of our product candidates. The physical equipment for the PRINT technology requires a relatively small footprint, low capital investment and minimal operating costs. We believe our manufacturing facilities comply with the FDA's current good manufacturing practices, or cGMP, requirements.
- ***We have a strong proprietary position through a combination of patents, trade secrets, proprietary know-how and licensing arrangements.*** We protect our PRINT technology and the resulting engineered particles through a combination of patents, trade secrets, proprietary know-how and licensing arrangements. We have an active patent strategy that covers major geographic markets, including the United States, Europe and Japan. As of December 31, 2018, our patent portfolio, which includes patents and patent applications we own or co-own, as well as patents and patent applications we have licensed from third parties, such as the University of North Carolina at Chapel Hill, or UNC, comprises 112 issued patents and 51 pending patent applications worldwide. As we develop new product candidates, either independently or with collaborators, we will seek additional patent protection.
- ***We have strong capabilities in pharmaceutical research and clinical development.*** Our research and development team includes 25 employees as of December 31, 2018, led by our senior management, and has extensive experience in clinical development and pharmaceutical research and development activities in our specific areas of research interest.
- ***We have a seasoned management team.*** Our team includes industry veterans with significant experience in drug discovery, development and commercialization. Members of our leadership team have worked across different segments of the pharmaceutical industry, including branded and generic pharmaceuticals, medical devices and manufacturing services. Prior to joining us, our Chief Executive Officer and director, Neal Fowler, served as president of Centocor, Inc., a subsidiary of Johnson & Johnson that is focused on the development and commercialization of biomedicines used to treat chronic inflammatory diseases. Additionally, our Chief Operations Officer, Robert Lippe, previously served as executive vice president of operations and chief operations officer at Alexza Pharmaceuticals, Inc. Furthermore, our Senior Vice President, Product Development, Dr. Robert Roscigno, previously served as the executive vice president of GeNO, LLC, where he led the clinical development team working on a novel nitric oxide delivery system, and before that he served as the president and chief operating officer of Lung Rx, Inc., where he was part of the team responsible for bringing Tyvaso through Phase 3 development, and he previously served in multiple leadership positions at United Therapeutics and its subsidiaries, contributing to the successful development and worldwide commercialization of Remodulin™, which is treprostinil administered through subcutaneous or intravenous infusion, for the treatment of PAH. We believe that their experience enables us to evaluate opportunities and build collaboration arrangements that match the breadth of the potential applications for our PRINT technology.

Our Product Candidates

LIQ861

Our lead product candidate, LIQ861, is an inhaled dry powder formulation of treprostinil designed using our PRINT technology to enhance deep-lung delivery using a convenient DPI for the treatment of PAH. We believe LIQ861 can overcome the limitations of current inhaled therapies and has the potential to maximize the therapeutic benefits of treprostinil in treating PAH by safely delivering higher doses into the lungs. If approved, we believe LIQ861 will have the potential to increase the number of patients using the inhaled route of treatment for PAH by providing the benefits of

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inhaled prostacyclin therapy earlier in a patient's disease progression as well as delaying the burden of starting continuously infused products.

Background on PAH

PAH is a chronic, progressive disease caused by the hardening and narrowing of pulmonary arteries that can lead to right heart failure and eventually death. Prostacyclin is a vasoactive mediator essential to normal lung function that is deficient in patients with PAH. With PAH, the elevated pressure in the pulmonary arteries strains the right side of the heart as it pumps blood to the lungs. The extra stress causes the heart to enlarge and become less flexible, compromising its ability to push blood out of the heart through the lungs and into the rest of the body. PAH initially presents as exertional dyspnea, lethargy and fatigue and may be confused with other disease states with similar symptoms. PAH often goes undiagnosed or misdiagnosed until symptoms become severe, with the mean time from onset of symptoms to correct diagnosis being more than two years in the United States. As PAH progresses and right ventricular failure develops, exertional chest pain, or angina, exertional syncope and peripheral edema may develop. Following confirmation of diagnosis based on hemodynamic parameters, treatment is recommended to lower pulmonary pressures and treat the symptoms of PAH.

PAH is part of a larger classification of pulmonary hypertension, or PH, which is divided into five groups based on the criteria of the World Health Organization, or WHO, as defined at the 5th World Symposium on Pulmonary Hypertension in Nice, France. WHO Group I is comprised of individuals with PAH.

PAH is a rare disease, with an estimated prevalence in the United States expected to be approximately 30,000 patients by 2020. Today, the mean age of diagnosis is 50 years according to both French and U.S. registries, with more women being diagnosed with PAH than men. Patients may have idiopathic PAH, in which no underlying cause can be determined, or a heritable form of the disease. A large number of PAH patients also have associated comorbidities such as congenital heart disease, HIV, connective tissue diseases like scleroderma, liver diseases, systemic hypertension, obesity, clinical depression, non-PAH related obstructive airways, sleep apnea and diabetes.

Due to delayed diagnosis, many patients already have an advanced form of PAH, requiring aggressive treatment combining multiple classes of therapy. The severity of PAH may be classified according to the heart failure guidelines of the New York Heart Association, or NYHA, based on how much patients are limited during physical activity and described by the American Heart Association as follows:

- NYHA Class I — No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea, which is shortness of breath.
- NYHA Class II — Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation or dyspnea.
- NYHA Class III — Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation or dyspnea.
- NYHA Class IV — Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

As reported by Decision Resources Group, gross revenue in the U.S. market for PAH drug therapies in 2017 was estimated to be \$3.7 billion. Of such amount, \$2.1 billion was generated from patients in NYHA Class III, \$1.2 billion was generated from patients in NYHA Class II and an aggregate of \$0.4 billion was generated from patients in NYHA Classes I and IV.

As the disease progresses, these symptoms cause significant negative impact on the quality of life of patients, limiting their ability to do common daily activities, including work, travel and previous hobbies. Patients also describe the

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emotional toll of PAH, including fear, frustration, embarrassment and stigma. The burden of care associated with currently available treatments can add further logistical and emotional burden to the patients.

Current Therapies and Their Limitations

There is currently no cure for PAH. The goals of existing treatments are to alleviate symptoms, maintain or improve NYHA functional class, delay disease progression and improve quality of life. Inhaled therapies are generally prescribed for, but not limited to, patients in NYHA Class II and Class III. Approved drugs target three distinct molecular pathways that have been implicated in the disease process: the prostacyclin pathway, the nitric oxide pathway and the endothelin pathway. Drugs targeting each of these pathways are used alone or in combination with each other to treat patients with PAH. Prostacyclin deficiency in the lung is a central dysfunction in PAH, but can be supplemented with prostacyclin analogs. Prostacyclin deficiency can also be managed with a recently approved selective IP prostacyclin receptor agonist, selexipag. Nitric oxide deficiency can be treated with phosphodiesterase-5, or PDE5, inhibitors, which target a specific enzyme, increasing vasodilation. Endothelin overexpression in PAH patients causes vasoconstriction of pulmonary vasculature, but can be treated with endothelin receptor antagonists, or ERAs. Many physicians start their PAH patients on oral PDE5 inhibitors, oral ERAs or both. Drugs targeted to the prostacyclin pathway are usually added to these oral therapies, but can be used alone.

Drugs targeting the prostacyclin pathway are central to PAH therapy. Prostacyclin is essential to normal lung function. In healthy people, prostacyclin, which is a vasoactive mediator, is continually released by lungs into arterial circulation to bind different receptors for different effects to regulate vessel tone, including direct vasodilation of pulmonary arteries, inhibition of the proliferation of smooth muscle cells within arteries and inhibition of platelet aggregation. To supplement the deficiency of prostacyclin in patients with PAH, several prostacyclin analogs have been developed including epoprostenol, which is administered intravenously; treprostinil, which can be administered intravenously, subcutaneously or in nebulized or oral formulations; and iloprost, which can be administered intravenously or in nebulized form. A new class of drugs called selective IP prostacyclin receptor agonists help stimulate some of the mechanisms that would otherwise be promoted by prostacyclin or an analog. Selexipag is an oral drug and the only approved molecule in this new class.

The goal of treatment targeting the prostacyclin pathway is to maximize a patient's exposure to the highest tolerable level of drug. Prostacyclin analogs, like treprostinil, have been developed for continuous infusion, either intravenously or subcutaneously, inhalation using a nebulizer and oral administration in the form of tablets. The maximal efficacy benefit of any one drug in the prostacyclin pathway is partially limited by its specific safety profile. Drugs treating the prostacyclin pathway, including oral treprostinil and IP prostacyclin receptor agonists such as selexipag, are limited by side effects from binding of the drug to receptors in non-targeted tissues, such as the gut and nerves, which can cause diarrhea, nausea and jaw pain. Nebulized solutions can have side effects including cough and upper airway irritation and pain caused by their topical irritant properties, which limits the amount of drug that can be given to the patient. As the disease progresses, patients will require continuous prostacyclin infusion to maximize drug exposure. Infusion pumps present unique risks related to infusion site pain and the risk of blood stream infections, and increase significant limitations on the quality of life of patients.

Delivering prostacyclin analogs locally to the lungs by inhalation has been effective and generates fewer systemic side effects. Inhalation of prostacyclin analogs supplements the endogenous production of prostacyclin where it is normally synthesized, near the targeted pulmonary arteries. As a result, inhalation of prostacyclin analogs helps avoid adverse events related to off-target tissues and takes advantage of binding key prostacyclin receptors that are preferentially expressed in the lung. The only inhaled prostacyclin analogs approved by the FDA are Tyvaso and Ventavis, which both require nebulizers.

Decision Resources Group reported that more than 80% of PAH patients on inhaled therapy in the United States used Tyvaso in 2017. United Therapeutics reported approximately \$373 million in total sales of Tyvaso in the United States. Tyvaso is approved in the United States and Israel but is not approved in Europe and Japan. Tyvaso is indicated for the treatment of PAH to improve exercise ability. The maximum recommended dose of Tyvaso is 54 mcg, delivered four times daily from a proprietary nebulizer, requiring nine breaths for each dose. In a long-term open-label extension study

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of Tyvaso, patients continued treatment for a mean duration of 2.3 years, with 89% of patients achieving the target dose of 54 mcg, delivered in nine breaths, and 42% achieving a dose of 72 mcg, delivered in 12 breaths.

Ventavis is approved in the United States, Europe and Japan. Ventavis is nebulized six to nine times a day during waking hours, no more than once every two hours, and takes six to ten minutes to administer per use. Ventavis is a synthetic analog of prostacyclin indicated for the treatment of PAH to improve a composite endpoint consisting of exercise tolerance, symptoms and lack of deterioration.

Tyvaso and Ventavis require the use of proprietary nebulizers. Patients must follow specific instructions to set up and operate the device, clean the device daily, locate a power source or use a battery to operate the device, and carry the device and its associated accessories around in a large carrying case, along with distilled water, to administer the treatment throughout the day. As a result, the use of these approved inhaled prostacyclin therapies is typically limited to patients who have not responded to oral medications that target the three pathways. The current medical practice is to administer both an inhaled drug product and the patient's existing oral ERA and/or PDE5 drug product concurrently, instead of withdrawing the administration of the oral drug product upon initiation of the inhaled drug product.

Potential Benefits of Our Approach

We believe LIQ861 can overcome the limitations of current nebulized therapies and has the potential to maximize the therapeutic benefits of treprostinil in treating PAH by safely delivering higher doses into the lungs using a convenient, palm-sized, disposable DPI. In our Phase 1 trial, LIQ861 was well-tolerated at doses approximately twice as high as the maximum recommended dosage of Tyvaso. These higher doses of inhaled dry powder treprostinil can also be administered in fewer breaths. Each dose of LIQ861 can be administered in one to four breaths, compared to nine breaths for the maximum recommended dosage of Tyvaso. Additionally, we believe LIQ861 may have the potential to improve overall patient adherence and quality of life by offering the convenience of a discrete, palm-sized, disposable DPI. In our market research, patients expressed a preference for a DPI product, noting that it can fit easily into a purse, minimize hassle while traveling and reduce the breaths and time associated with their current nebulized treatments.

The advantages of the LIQ861 product profile are enabled by the PRINT technology. Each LIQ861 particle is designed to enhance delivery and deep-lung penetration. LIQ861 particles are a precise size and highly uniform since particles are formed from mold cavities that exactly match each other. Competing technologies, such as spray-drying, create particles that have a broader variation in shape and size. As a result, particles farther from the mean target size would be too large or too small to reach the intended location in the deep-lung.

Inspired by a naturally occurring pollen, LIQ861 PRINT particles have a one micrometer trefoil-shape measured by an inscribed one micrometer circle as shown in the figure below. *In vitro* studies suggest that the uniformity of size and shape allow our inhaled particles to target delivery into the lungs while depositing less in the upper airways. Our independent control of the parameters of drug particles has enabled us to create the first clinically tested formulation that stabilizes treprostinil in an inhaled dry powder formulation.

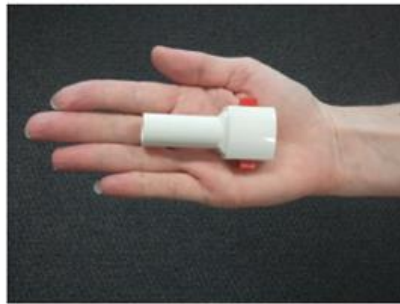
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The figures below depict LIQ861, with the figure on the left showing size and shape consistency among particles and the figure on the right showing their trefoil shape:



LIQ861 is administered using RS00 Model 8 DPI, a DPI manufactured by Plastiap S.p.A. There are products approved in the United States and Europe containing this device. This device and its variants have been used in at least eight marketed products globally since 2001, including Novartis's Foradil Aerolizer®, for the treatment of asthma and chronic obstructive pulmonary disease, or COPD.

The picture below shows the DPI used to administer LIQ861:



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Clinical Development

In March 2017, we completed a Phase 1 trial of LIQ861 in 57 healthy volunteers. In January 2018, we announced the initiation of INSPIRE, our pivotal open-label Phase 3 clinical trial, evaluating LIQ861 for the treatment of PAH in the United States. LIQ861 was observed to be well-tolerated at the two-week timepoint in PAH patients. The safety data at the two-week timepoint addresses the FDA's request for inclusion of such data in an NDA submission. During this two-week time period, LIQ861 was evaluated at capsule strengths up to 125 mcg treprostinil, with no study-drug related serious adverse events or dose-limiting toxicities observed. The INSPIRE study is designed to evaluate patients who have either been under stable treatment with nebulizer-delivered treprostinil for at least three months and are transitioned to LIQ861 under the protocol or who have been under stable treatment with no more than two non-prostacyclin oral PAH therapies for at least three months and have their treatment regimen supplemented with LIQ861 under the protocol. Patients adding LIQ861 to current non-prostacyclin oral therapies started at a capsule strength of 25 mcg treprostinil and those transitioned from nebulizer-delivered treprostinil at a stable dose were initiated at a capsule strength of LIQ861 lower than their current stable treprostinil dose. In both cases, LIQ861 was uptitrated in 25 mcg treprostinil incremental capsule strengths to symptom relief or the limit of tolerance. The primary objective of the study is to evaluate the long-term safety and tolerability of LIQ861. We are currently focusing our efforts on completing patient enrollment in our one-directional crossover sub-study of at least 18 patients to compare bioavailability and pharmacokinetics of treprostinil as the patients transition from Tyvaso to LIQ861. After review of an initial cohort of patients in our open-label INSPIRE trial, we amended the INSPIRE protocol to adjust pharmacokinetics sub-study dosing levels of LIQ861 to more closely match Tyvaso dosing levels on an emitted dose basis. We reported positive interim two-week safety data in January 2019 and expect to report pharmacokinetics results in the second quarter of 2019. We intend to conduct additional clinical work in support of our marketing and commercial activities in advance of our U.S. launch for LIQ861, including maintaining patients on LIQ861 up to our U.S. launch and collecting data relating to the effects of LIQ861 on hemodynamic measurements. In the United States, we plan to seek approval of our NDA under the 505(b)(2) regulatory pathway, which would allow us to rely, in part, on the FDA's prior conclusions of efficacy and safety for Tyvaso and the active ingredient treprostinil, which has been approved in four different products administered through the continuous infusion, inhaled and oral routes. We are targeting an NDA submission to the FDA for LIQ861 in late 2019 which submission will include the two-week safety data, the available two-month safety and tolerability data and our bioavailability and pharmacokinetics results. We expect the NDA to also include additional data generated from our clinical studies on LIQ861 and any further safety data available at that time.

Results of Phase 1 Trial

We conducted a randomized, placebo-controlled, double-blind, Phase 1 trial in 57 healthy volunteer subjects to assess safety, tolerability and pharmacokinetics following a single administration of LIQ861 at treprostinil capsule strengths between 25 mcg and 150 mcg. The subjects were enrolled into six dose cohorts. Within each dose cohort, subjects were randomized to receive LIQ861 or a placebo.

Dose Selection

For the first-in-human study, the initial dose for LIQ861 was chosen based on the indicated dosing for the reference listed drug, Tyvaso. Independent investigations of particle emission using the RS00 Model 8 DPI and simulated inspiration of the bulk powder from a nebulizer led to a projection that a 25 mcg treprostinil capsule strength of LIQ861 dry powder inhalation would result in approximately similar treprostinil administration as three breaths of Tyvaso, or

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in the Registration Statement on Form S-8 (No. 333-226344) of Liquidia Technologies, Inc. of our report dated February 26, 2019 relating to the financial statements which appears in this Form 10-K.

/s/ PricewaterhouseCoopers LLP
Raleigh, North Carolina
February 26, 2019

CERTIFICATION OF THE PRINCIPAL EXECUTIVE OFFICER
PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Neal Fowler, certify that:

1. I have reviewed this annual report on Form 10-K of Liquidia Technologies, Inc. for the year ended December 31, 2018;
2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;
3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;
4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:
 - (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;
 - (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;
 - (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and
 - (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and
5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):
 - (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and
 - (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

February 26, 2019

/s/ Neal Fowler

Name: Neal Fowler
Chief Executive Officer
Title: (Principal Executive Officer)

CERTIFICATION OF THE PRINCIPAL FINANCIAL OFFICER
PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Kevin Gordon, certify that:

1. I have reviewed this annual report on Form 10-K of Liquidia Technologies, Inc. for the year ended December 31, 2018;
2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;
3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;
4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:
 - (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;
 - (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;
 - (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and
 - (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and
5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):
 - (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and
 - (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

February 26, 2019

/s/ Kevin Gordon

Name: Kevin Gordon

Title: President and Chief Financial Officer
(Principal Financial Officer)

Exhibit 32.1

CERTIFICATION OF THE PRINCIPAL EXECUTIVE OFFICER
PURSUANT TO 18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the annual report of Liquidia Technologies, Inc., a Delaware corporation (the "Company"), on Form 10-K for the year ended December 31, 2018, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I, Neal Fowler, Chief Executive Officer of the Company, hereby certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that, to my knowledge:

- (1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended; and
- (2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

February 26, 2019

/s/ Neal Fowler

Name: Neal Fowler
Title: Chief Executive Officer
(Principal Executive Officer)

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Exhibit 32.2

**CERTIFICATION OF THE PRINCIPAL FINANCIAL OFFICER
PURSUANT TO SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002**

In connection with the annual report of Liquidia Technologies, Inc., a Delaware corporation (the "Company"), on Form 10-K for the year ended December 31, 2018, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I, Kevin Gordon, Chief Financial Officer of the Company, hereby certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that, to my knowledge:

- (1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended; and
- (2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

February 26, 2019

/s/ Kevin Gordon

Name: Kevin Gordon

Title: President and Chief Financial Officer
(Principal Financial Officer)

EXHIBIT 7

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

(Mark One)

☒ ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended December 31, 2019

or

☐ TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the transition period from _____ to _____

Commission File Number: 001-38601
LIQUIDIA TECHNOLOGIES, INC.
(Exact Name of Registrant as Specified in Its Charter)

<u>Delaware</u> (State or Other Jurisdiction of Incorporation or Organization)	<u>20-1926605</u> (I.R.S. Employer Identification No.)
<u>419 Davis Drive, Suite 100</u> <u>Morrisville, North Carolina</u> (Address of Principal Executive Offices)	<u>27560</u> (Zip Code)

Registrant's telephone number, including area code: **(919) 328-4400**

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common stock, \$0.001 par value per share	LQDA	The Nasdaq Stock Market LLC

Securities registered pursuant to Section 12(g) of the Act: **None**

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☐ No ☒

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company" and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large Accelerated Filer ☐ Accelerated Filer ☒ Non-accelerated Filer ☐ Smaller Reporting Company ☒
Emerging Growth Company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act ☒

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☒

The aggregate market value of common stock held by non-affiliates of the registrant on June 28, 2019, which was the last business day of the registrant's most recently completed second fiscal quarter, was \$107,845,184 based on a \$8.00 closing price per share as reported on the Nasdaq Capital Market.

As of March 9, 2020, there were 28,368,464 shares of the registrant's common stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Liquidia Technologies, Inc. Definitive Proxy Statement with respect to the 2020 Annual Meeting of Stockholders to be filed pursuant to Regulation 14A within 120 days after the end of the fiscal year ended December 31, 2019 are incorporated by reference into Part III of this Annual Report on Form 10-K to the extent stated therein. Except with respect to information specifically incorporated by reference in the Form 10-K, each document incorporated by reference herein is deemed not to be filed as part hereof.

LIQUIDIA TECHNOLOGIES, INC.

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This annual report on Form 10-K includes our trademarks, trade names and service marks, such as Liquidia, the Liquidia logo and PRINT, or Particle Replication In Non-wetting Templates, which are protected under applicable intellectual property laws and are the property of Liquidia Technologies, Inc. This annual report also contains trademarks, trade names and service marks of other companies, which are the property of their respective owners. Solely for convenience, trademarks, trade names and service marks referred to in this annual report may appear without the ®, TM or SM symbols, but such references are not intended to indicate, in any way, that we will not assert, to the fullest extent under applicable law, our rights or the right of the applicable licensor to these trademarks, trade names and service marks. We do not intend our use or display of other parties' trademarks, trade names or service marks to imply, and such use or display should not be construed to imply, a relationship with, or endorsement or sponsorship of us by, these other parties.

- **Advance our local post-operative pain product candidate, LIQ865, through Phase 2-enabling toxicology studies into Phase 2 clinical trials.** We completed a Phase 1a clinical trial of LIQ865 in Denmark in 2017 and a Phase 1b clinical trial in the United States in 2018. We initiated Phase 2-enabling toxicology studies in 2019 to assess LIQ865 in multiple non-clinical tissue models. Results from a study to assess incision tensile strength after healing were acceptable and not statistically different from controls. A nonclinical study to examine soft tissue healing was also completed, and the results were acceptable and comparable to vehicle-treated, saline-treated, and Marcaine-treated sites. We believe this data supports progression to Phase 2 hernia repair studies. In a study to assess bone fracture healing, we observed dose-dependent delayed healing at the two LIQ865 doses studied; however, there were no adverse effects noted on surrounding soft tissues. Additional studies have been initiated with lower doses of LIQ865 to determine a NOAEL on bone healing. We will review the results from these toxicology studies, and if supportive, we intend to initiate Phase 2 proof-of-concept clinical trials, subject to availability of capital and other factors, during 2021. We believe LIQ865, if successfully developed and approved, has the potential to provide significantly longer local post-operative pain relief compared to currently marketed formulations of bupivacaine.
- **Secure regulatory approval and commercialize our products in the United States either ourselves or through partnership or licensing arrangements with other pharmaceutical companies, and globally through licensing arrangements with pharmaceutical companies.** We hold worldwide commercialization rights to LIQ861 and LIQ865. We are currently exploring opportunities to commercialize LIQ861 in the United States, subject to receiving regulatory approval, either by ourselves or through partnership or licensing arrangements with other pharmaceutical companies. With respect to LIQ865, after reviewing the results of all of our Phase 2-enabling toxicology studies, and subject to the availability of sufficient funding, we plan to evaluate whether to pursue continued internal development or to explore licensing arrangements with other pharmaceutical companies. Outside of the United States, we intend to pursue the regulatory approval and commercialization of LIQ861 and LIQ865 through licensing arrangements with pharmaceutical companies with regional expertise.
- **Expand our internal pipeline leveraging our PRINT technology.** We intend to continue targeting diseases where we believe our PRINT technology can improve the efficacy, safety and patient experience of current treatments that have been impaired by suboptimal drug product formulation and delivery. We plan to focus initially on the development of improved and differentiated drug products containing FDA-approved active pharmaceutical ingredients, or APIs, with proven efficacy and safety profiles eligible to use the 505(b)(2) regulatory pathway. In addition, we may expand our clinical development of LIQ861 and LIQ865, where appropriate, into broader indications or new applications.
- **Pursue strategic collaborations to maximize the value of products enabled by PRINT technology.** In addition to advancing our own internal product candidates, we have collaborated, and may consider collaborating, with pharmaceutical companies to develop their own product candidates across a wide range of therapeutic areas, molecule types and routes of administration, leveraging our PRINT technology. We believe that collaborating with pharmaceutical companies helps advance new PRINT capabilities, while adding to our intellectual property portfolio.

Our Competitive Strengths

We believe that we have several key strengths that have contributed to the development of our business and that will help us to realize our goal of becoming a biopharmaceutical company across research, development and commercialization activities. Our competitive strengths include:

- ***Our PRINT technology gives us the capability to overcome the constraints of conventional formulation and production methods and can be applied broadly across therapeutic areas, molecule types and routes of administration.*** Our PRINT technology allows us to precisely engineer drug particles in a wide variety of compositions, sizes and shapes and achieve a high level of control over the physical and chemical characteristics of drug particles, as compared to conventional formulation and production methods. PRINT particles can be designed to address specific pharmacological or therapeutic objectives, such as enhancing the route of administration, improving solubility, enhancing stability or extending therapeutic effects. Using our PRINT technology, we are able to engineer, among others, small molecule and biologic particles, single agent drug and combination drug particles and vaccine particles to improve efficacy, safety and convenience for patients. Our internal pipeline strategy is currently focused on developing proprietary innovations to currently approved drug products in order to minimize development risks and increase speed to market. In particular, we have designed LIQ861 to maximize the therapeutic benefits of treprostinil in treating PAH by safely delivering higher doses into the lungs using a convenient, palm-sized DPI. We believe that this may lead to a more attractive product profile with a more convenient method of administering the drug, as compared to the currently available inhaled therapies. We have also designed LIQ865 with the intention of providing patients with local post-operative analgesia for three to five days. We believe this would provide a longer period of pain relief than the currently available local-acting pain drugs and thereby reduce reliance on opioids and non-steroidal anti-inflammatory drugs, or NSAIDs, for local post-operative pain management.
- ***We have scaled operations with rapid and cost-effective transition to clinical development and commercial production.*** We believe our research and development operations and PRINT technology allow us to transition rapidly and cost-effectively from laboratory to clinical development and ultimately commercial-scale manufacture of drug particles. Utilizing well-established techniques from other roll-to-roll manufacturing processes, we have scaled PRINT technology to support the quality and quantity needs for clinical and, we believe, commercial production of our product candidates. The manufacturing equipment for the PRINT technology requires a relatively small footprint, low capital investment and minimal operating costs. We believe our manufacturing facilities comply with the FDA's current good manufacturing practices, or cGMP, requirements.
- ***We have a strong proprietary position through a combination of patents, trade secrets, proprietary know-how and licensing arrangements.*** We protect our PRINT technology and the resulting engineered particles through a combination of patents, trade secrets, proprietary know-how and licensing arrangements. We have an active patent strategy that covers major geographic markets, including the United States, Europe and Japan. As of December 31, 2019, our patent portfolio, which includes patents and patent applications we own or co-own, as well as patents and patent applications we have licensed from third parties, such as the University of North Carolina at Chapel Hill, or UNC, comprises 127 issued patents and 32 pending patent applications worldwide. As we develop new product candidates, either independently or with collaborators, we will seek additional patent protection.
- ***We have strong capabilities in pharmaceutical research and clinical development.*** Our research and development team includes 22 employees as of December 31, 2019, led by our senior management, and has extensive experience in clinical development and pharmaceutical research and development activities in our specific areas of research interest.
- ***We have a seasoned management team.*** Our management team includes industry veterans with significant experience in drug discovery, development and commercialization. Members of our leadership team have worked across different segments of the pharmaceutical industry, including branded and generic pharmaceuticals, medical devices and manufacturing services. Prior to joining us, our Chief Executive Officer and director, Neal Fowler, served as president of Centocor, Inc., a subsidiary of Johnson & Johnson that is focused on the development and commercialization of biomedicines used to treat chronic inflammatory diseases. Additionally, our Chief Operations Officer, Robert Lippe, previously served as executive vice president of operations and chief operations officer at Alexza Pharmaceuticals, Inc. Furthermore, our Senior Vice President, Product Development, Dr. Robert Roscigno, previously served as the president and chief operating officer of Lung Rx, Inc., where he was a member of the team responsible for bringing Tyvaso through Phase 3 development, and held multiple leadership positions at United Therapeutics and its subsidiaries, where he contributed to the successful development and worldwide commercialization of Remodulin™, a parenteral formulation of treprostinil. We believe that the experience of these individuals and other members of our management team enables us to evaluate opportunities and build collaboration arrangements that match the breadth of the potential applications for our PRINT technology.

Our Product Candidates

LIQ861

Our lead product candidate, LIQ861, is an inhaled dry powder formulation of treprostinil designed using our PRINT technology to enhance deep-lung delivery using a convenient DPI for the treatment of PAH. We believe LIQ861 can overcome the limitations of current inhaled therapies and has the potential to maximize the therapeutic benefits of treprostinil in treating PAH by safely delivering higher doses into the lungs. If approved, we believe LIQ861 will have the potential to increase the number of patients using the inhaled route of administration for PAH by providing the benefits of inhaled prostacyclin therapy earlier in a patient's disease progression as well as delaying the burden of starting continuously infused agents.

Background on PAH

PAH is a chronic, progressive disease caused by hardening and narrowing of the pulmonary arteries that can lead to right heart failure and eventually death. Prostacyclin is a vasoactive mediator essential to normal lung function that is deficient in patients with PAH. With PAH, the elevated pressure in the pulmonary arteries strains the right side of the heart as it pumps blood to the lungs. The extra stress causes the heart to enlarge and become less flexible, compromising its ability to pump blood through the lungs and to the rest of the body. PAH initially presents as exertional dyspnea, lethargy and fatigue and may be confused with other disease states with similar symptoms. PAH often goes undiagnosed or misdiagnosed until symptoms become severe, with the mean time from onset of symptoms to correct diagnosis being more than two years in the United States. As PAH progresses and right ventricular failure develops, exertional chest pain, or angina, exertional syncope and peripheral edema may develop. Following confirmation of the diagnosis based on hemodynamic parameters, treatment is recommended to lower pulmonary arterial pressures and treat the symptoms of PAH.

PAH is part of a larger classification of pulmonary hypertension, or PH, which is divided into five groups based on the criteria of the World Health Organization, or WHO, as defined at the 5th World Symposium on Pulmonary Hypertension. WHO Group I is comprised of individuals with PAH.

PAH is a rare disease, with an estimated prevalence in the United States of approximately 30,000 patients. The mean age of diagnosis is 50 years according to both French and U.S. registries, with more women being diagnosed with PAH than men. Patients may have idiopathic PAH, in which no underlying cause can be determined, or a heritable form of the disease. A large number of PAH patients also have associated comorbidities such as congenital heart disease, HIV, connective tissue diseases like scleroderma, liver diseases, systemic hypertension, obesity, clinical depression, non-PAH related obstructive airways, sleep apnea and diabetes.

Due to delayed diagnosis, many patients already have an advanced form of PAH, requiring aggressive treatment combining multiple classes of therapy. The severity of PAH may be classified according to the heart failure guidelines of the NYHA based on the degree of limitation of physical activity and described by the American Heart Association as follows:

- NYHA Class I — No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea, which is shortness of breath.
- NYHA Class II — Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation or dyspnea.
- NYHA Class III — Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation or dyspnea.

- NYHA Class IV — Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

As the disease progresses, these symptoms cause a significant negative impact on quality of life, limiting the ability to perform common daily activities, including work, travel and previous hobbies. Patients also describe the emotional toll of PAH, including fear, frustration, embarrassment and stigma. The burden of care associated with currently available treatments can add further logistical and emotional burden to the patients.

Current Therapies and Their Limitations

There is currently no cure for PAH. The goals of existing treatments are to alleviate symptoms, maintain or improve NYHA functional class, delay disease progression and improve quality of life. Inhaled therapies are generally prescribed for, but not limited to, patients in NYHA Class II and Class III. Approved drugs target three distinct molecular pathways that have been implicated in the disease process: the prostacyclin pathway, the nitric oxide pathway and the endothelin pathway. Drugs targeting each of these pathways are used alone or in combination with each other to treat patients with PAH. Prostacyclin deficiency in the lung is a central dysfunction in PAH, but can be supplemented with prostacyclin analogs. Prostacyclin deficiency can also be managed with a recently approved selective IP prostacyclin receptor agonist, selexipag. Nitric oxide deficiency can be treated with phosphodiesterase-5, or PDE5, inhibitors, which target a specific enzyme, increasing vasodilation. Endothelin overexpression in PAH patients causes vasoconstriction of pulmonary vasculature, but can be treated with endothelin receptor antagonists, or ERAs. Many physicians start their PAH patients on oral PDE5 inhibitors, oral ERAs or both. Drugs targeted to the prostacyclin pathway are usually added to these oral therapies, but can be used alone.

Drugs targeting the prostacyclin pathway are central to PAH therapy. Prostacyclin is essential to normal lung function. In healthy people, prostacyclin, which is a vasoactive mediator, is continually released by the lungs into the pulmonary arterial circulation, where it affects the regulation of vascular tone, including through direct vasodilation of pulmonary arteries, inhibition of the proliferation of smooth muscle cells within arteries and inhibition of platelet aggregation. To supplement the deficiency of prostacyclin in patients with PAH, several prostacyclin analogs have been developed including epoprostenol, which is administered intravenously; treprostinil, which can be administered intravenously, subcutaneously or in nebulized or oral formulations; and iloprost, which can be administered intravenously or in nebulized form. A new class of drugs called selective IP prostacyclin receptor agonists help stimulate some of the mechanisms that would otherwise be promoted by prostacyclin or an analog. Selexipag, an oral agent, is the only approved drug in this new class.

The goal of treatment targeting the prostacyclin pathway is to maximize a patient's exposure to the highest tolerable level of drug. Prostacyclin analogs, like treprostinil, have been developed for continuous infusion, either intravenously or subcutaneously, inhalation using a nebulizer and oral administration in the form of tablets. The maximal efficacy benefit of any one drug in the prostacyclin pathway is partially limited by its specific safety profile. Drugs exerting their effect through the prostacyclin pathway, including oral treprostinil and IP prostacyclin receptor agonists such as selexipag, are limited by side effects from binding of the drug to receptors in non-targeted tissues, such as the gastrointestinal tract and nerves, which can cause diarrhea, nausea and jaw pain. Nebulized solutions can have side effects including cough, upper airway irritation and pain caused by their topical irritant properties, which limits the amount of drug that can be given to the patient. As the disease progresses, patients require continuous prostacyclin infusion to maximize drug exposure. However, infusion pumps can cause side effects related to infusion site pain and risk of infection, while also adversely affecting quality of life.

Delivering prostacyclin analogs locally to the lungs by inhalation has been effective and causes fewer systemic side effects. Inhalation of prostacyclin analogs supplements the endogenous production of prostacyclin where it is normally synthesized, near the targeted pulmonary arteries. As a result, inhalation of prostacyclin analogs helps avoid side effects related to off-target tissues and takes advantage of binding key prostacyclin receptors that are preferentially expressed in the lung. The only inhaled prostacyclin analogs approved by the FDA are Tyvaso and Ventavis, which both require nebulizers.

Tyvaso (treprostinil) is approved in the United States and Israel, but is not approved in Europe and Japan. Tyvaso is indicated for the treatment of PAH to improve exercise ability. The maximum recommended dose of Tyvaso is 54 mcg, delivered four times daily from a proprietary nebulizer, requiring nine breaths for each dose. In a long-term open-label extension study of Tyvaso, patients continued treatment for a mean duration of 2.3 years, with 89% of patients achieving the target dose of 54 mcg, delivered in nine breaths, and 42% achieving a dose of 72 mcg, delivered in 12 breaths. It has been reported that more than 80% of PAH patients on inhaled therapy in the United States use Tyvaso. United Therapeutics reported approximately \$415 million in sales of Tyvaso in 2019.

Ventavis (iloprost) is approved in the United States, Europe and Japan. Ventavis is a synthetic analog of prostacyclin indicated for the treatment of PAH to improve a composite endpoint consisting of exercise tolerance, symptoms and lack of deterioration. Ventavis is administered with a proprietary nebulizer six to nine times per day during waking hours, no more than once every two hours, and takes six to ten minutes to administer per use.

Tyvaso and Ventavis both require the use of proprietary nebulizers. Patients must follow specific instructions to set up and operate the device, clean the device daily, locate a power source or use a battery to operate the device, and carry the device and its associated accessories around in a large carrying case, along with distilled water, to administer the treatment throughout the day. As a result, the use of these approved inhaled prostacyclin therapies is typically limited to patients who have not responded to oral medications that target the three pathways. Current medical practice is to add an inhaled drug to the patient's existing oral ERA and/or PDE5 treatment regimen, rather than withdrawing the oral drug upon initiation of the inhaled drug.

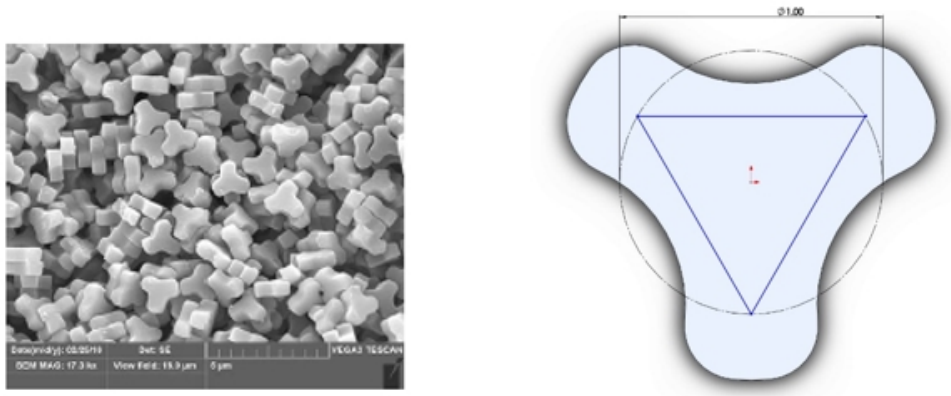
Potential Benefits of Our Approach

We believe LIQ861 can overcome the limitations of current nebulized therapies and has the potential to maximize the therapeutic benefits of treprostinil in treating PAH by safely delivering higher doses into the lungs using a convenient, palm-sized DPI. In our clinical trials, LIQ861 has been well-tolerated at doses approximately twice as high as the maximum recommended dosage of Tyvaso. These higher doses of inhaled dry powder treprostinil can also be administered in one to four breaths, compared to nine breaths for the maximum recommended dose of Tyvaso. Additionally, we believe LIQ861 may have the potential to improve overall patient adherence by offering the convenience of a discrete, palm-sized DPI. In our market research, patients expressed a preference for a DPI product, noting that it can fit easily into a purse, minimize hassle while traveling and reduce the breaths and time associated with their current nebulized treatments.

The advantages of the LIQ861 product profile are enabled by our PRINT technology. Each LIQ861 particle is designed to enhance delivery and deep-lung penetration. LIQ861 particles are a precise size and highly uniform shape, since particles are formed from mold cavities that exactly match each other. Competing technologies, such as spray-drying, create particles that have a broader variation in size and shape. As a result, particles farther from the mean target size would be too large or too small to reach the intended location in the deep-lung.

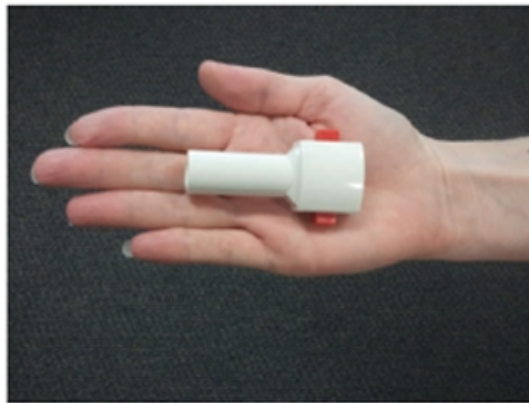
Inspired by a naturally occurring pollen, LIQ861 PRINT particles have a one micrometer trefoil-shape measured by an inscribed one micrometer circle as shown in the figure below. *In vitro* studies suggest that the uniformity of size and shape allow our inhaled particles to target delivery into the lungs with less deposition in the upper airways. Our independent control of the parameters of drug particles has enabled us to create the first clinically tested therapeutic that stabilizes treprostinil in an inhaled dry powder formulation.

The figures below depict LIQ861, with the figure on the left showing size and shape consistency among particles and the figure on the right showing their trefoil shape:



LIQ861 is administered using the RS00 Model 8 DPI, which is manufactured by Plastiap S.p.A. This device and its variants have been used in at least eight marketed products globally since 2001, including Novartis's Foradil Aerolizer® for the treatment of asthma and chronic obstructive pulmonary disease, or COPD.

The picture below shows the DPI used to administer LIQ861:



Clinical Development

The INSPIRE study was designed to evaluate patients who have either been under stable treatment with nebulizer-delivered treprostinil for at least three months and are transitioned to LIQ861 under the protocol or who have been under stable treatment with no more than two non-prostacyclin oral PAH therapies for at least three months and have their treatment regimen supplemented with LIQ861 under the protocol. The primary objective of the study was to evaluate the long-term safety and tolerability of LIQ861.

In the United States, we submitted an NDA under the 505(b)(2) regulatory pathway in January 2020. The 505(b)(2) pathway allows us to rely, in part, on the FDA's prior conclusions of efficacy and safety for Tyvaso, and the active ingredient treprostinil (which has been the active ingredient in several different products, in total, approved by the FDA, with routes of administration including continuous infusion, inhaled and oral routes).

Clinical Development

We have developed LIQ861 under the 505(b)(2) regulatory pathway, which allows for an accelerated development program based upon establishing safety, tolerability, and comparative bioavailability to a reference listed drug, which for LIQ861 is Tyvaso. Our clinical development program has consisted of two principal studies. The first of these was a Phase 1 study in healthy volunteers that was designed to assess the safety, tolerability and pharmacokinetic parameters of LIQ861 in healthy volunteers. After an end of Phase 1 meeting with the FDA, we proceeded directly to a pivotal Phase 3 study, without being required to conduct a Phase 2 study. In addition, we conducted two supplementary pharmacokinetic studies in healthy volunteers. The results of these studies, which serve as the basis for our NDA submission, are described below.

Phase 1 Trial

We conducted a randomized, placebo-controlled, double-blind, Phase 1 trial in 57 healthy volunteers to assess safety, tolerability and pharmacokinetics following a single administration of LIQ861 at treprostinil capsule strengths between 25 mcg and 150 mcg. The subjects were enrolled into six dose cohorts. Within each dose cohort, subjects were randomized to receive LIQ861 or a placebo.

Dose Selection

For the first-in-human study, the initial dose for LIQ861 was chosen based on the indicated dosing for the reference listed drug, Tyvaso. Independent investigations of particle emission using the RS00 Model 8 DPI and simulated inspiration of the bulk powder from a nebulizer led to a projection that a 25 mcg treprostinil capsule strength of LIQ861 dry powder inhalation would result in approximately similar treprostinil administration as three breaths of Tyvaso, or 18 mcg of treprostinil, the lowest approved dose through nebulization. The following table shows the doses of LIQ861 tested along with our estimate of the equivalent Tyvaso dose.

Estimated TRE Dose from LIQ861				Estimated TRE Dose from Tyvaso	
Capsule (LIQ861 fill wt.)	Approx. Capsule (TRE fill wt.)	Approx. Emitted Dose	Breaths ¹	Approx. Emitted Dose	Breaths ²
5 mg	25 mcg	20 mcg	1-2	18 mcg	3
10 mg	50 mcg	40 mcg	1-2	36 mcg	6
15 mg	75 mcg	60 mcg	1-2	54 mcg	9
20 mg	100 mcg	80 mcg	1-2	Above maximum recommended dose	
(10 mg + 15 mg)	125 mcg ¹	100 mcg	2-4	Above maximum recommended dose	
(15 mg + 15 mg)	150 mcg ¹	120 mcg	2-4	Above maximum recommended dose	

- (1) LIQ861 capsule treprostinil strength doses between 25 mcg and 100 mcg are single capsules. LIQ861 capsule treprostinil strength doses of 125 mcg and 150 mcg are two capsules, but, if approved, they could be developed as single capsules and therefore only require one to two breaths.
- (2) Tyvaso (treprostinil) full prescribing information: initial dosage: 3 breaths (18 mcg); maximum recommended dosage: 9 breaths (54 mcg).

Our conclusion from this study is that the capsule strength of 75 mcg of LIQ861 is approximately equivalent to the maximum recommended dose of 54 mcg, or nine breaths, of Tyvaso, and the capsule strength of 150 mcg of LIQ861 is approximately double the maximum recommended dose of Tyvaso.

Safety and Tolerability

In the Phase 1 clinical trial, we escalated the treprostinil capsule strength of LIQ861 progressively from 25 mcg to 150 mcg. There were no dose-limiting toxicities at the highest dose evaluated. We noted no serious adverse events and all reported treatment-emergent adverse events, or TEAEs, related to the treatment were mild. The most frequent adverse event reported by subjects receiving LIQ861 was mild cough and throat irritation.

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in the Registration Statements on Form S-3 (No. 333-233438 and No. 333-236227) and Form S-8 (No. 333-226344, No. 333-230077 and No. 333-233224) of Liquidia Technologies, Inc. of our report dated March 16, 2020 relating to the financial statements which appears in this Form 10-K.

/s/ PricewaterhouseCoopers LLP
Raleigh, North Carolina
March 16, 2020

**CERTIFICATION OF THE PRINCIPAL EXECUTIVE OFFICER
PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002**

I, Neal Fowler, certify that:

1. I have reviewed this Annual Report on Form 10-K of Liquidia Technologies, Inc.;
2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;
3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;
4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15(d)-15(f)) for the registrant and have:
 - a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;
 - b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;
 - c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and
 - d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and
5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):
 - a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and
 - b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 16, 2020

By: /s/ Neal Fowler
Name: Neal Fowler
Title: Chief Executive Officer
(Principal Executive Officer)

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**CERTIFICATION OF THE PRINCIPAL FINANCIAL OFFICER
PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002**

I, Richard D. Katz, M.D., certify that:

1. I have reviewed this Annual Report on Form 10-K of Liquidia Technologies, Inc.;
2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;
3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;
4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15(d)-15(f)) for the registrant and have:
 - a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;
 - b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;
 - c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and
 - d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and
5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):
 - a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and
 - b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 16, 2020

By: /s/ Richard D. Katz, M.D.
Name: Richard D. Katz, M.D.
Title: Chief Financial Officer
(Principal Financial Officer)

**CERTIFICATION OF THE PRINCIPAL EXECUTIVE OFFICER
PURSUANT TO SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002**

In connection with the Annual Report of Liquidia Technologies, Inc., a Delaware corporation (the “Company”), on Form 10-K for the year ended December 31, 2019, as filed with the Securities and Exchange Commission on the date hereof (the “Report”), I, Neal Fowler, Chief Executive Officer of the Company, hereby certify, pursuant to 18 U.S.C. § 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to my knowledge:

1. The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended; and
2. The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: March 16, 2020

By: /s/ Neal Fowler
Name: Neal Fowler
Title: Chief Executive Officer
(Principal Executive Officer)

Exhibit 32.2

**CERTIFICATION OF THE PRINCIPAL FINANCIAL OFFICER
PURSUANT TO SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002**

In connection with the Annual Report of Liquidia Technologies, Inc., a Delaware corporation (the “Company”), on Form 10-K for the year ended December 31, 2019, as filed with the Securities and Exchange Commission on the date hereof (the “Report”), I, Richard D. Katz, M.D., Chief Financial Officer of the Company, hereby certify, pursuant to 18 U.S.C. § 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to my knowledge:

1. The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended; and
2. The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: March 16, 2020

By: /s/ Richard D. Katz, M.D.
Name: Richard D. Katz, M.D.
Title: Chief Financial Officer
(Principal Financial Officer)

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EXHIBIT 8

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use YUTREPIA™ safely and effectively. See full prescribing information for YUTREPIA™.

YUTREPIA™ (treprostinil) inhalation powder, for oral inhalation
Initial U.S. Approval: 2002

INDICATIONS AND USAGE

YUTREPIA is a prostacyclin mimetic indicated for the treatment of:

- Pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability. Studies establishing effectiveness predominately included patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%). (1.1)
- Pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability. The study establishing effectiveness predominately included patients with etiologies of idiopathic interstitial pneumonia (IIP) (45%) inclusive of idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE) (25%), and WHO Group 3 connective tissue disease (22%). (1.2)

DOSAGE AND ADMINISTRATION

- For oral inhalation only. Do not swallow YUTREPIA capsules. Use only with the provided inhaler (2)
- YUTREPIA should be administered 3 to 5 times per day. The contents of each capsule can be inhaled in 2 breaths. (2.1)
- See *Dosage and Administration* for full instructions on dosing of patients who are treprostinil-naïve or transitioning from treprostinil inhalation solution to YUTREPIA (2.1)

DOSAGE FORMS AND STRENGTHS

YUTREPIA inhalation powder contained in capsule is available in 4 strengths: 26.5 mcg, 53 mcg, 79.5 mcg, 106 mcg (3)

CONTRAINDICATIONS

WARNINGS AND PRECAUTIONS

- Treprostinil may cause symptomatic hypotension. (5.1)
- Treprostinil inhibits platelet aggregation and increases the risk of bleeding. (5.2)
- Dosage adjustments may be necessary if inhibitors or inducers of CYP2C8 are added or withdrawn. (5.3, 7.1)
- May cause bronchospasm: Patients with a history of hyperreactive airway disease may be more sensitive. (5.4)

ADVERSE REACTIONS

Most common adverse reactions with YUTREPIA (≥10%) are cough, headache, throat irritation, and dizziness. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Liquidia Technologies, Inc. at 1-XXX-XXX-XXXX or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling (Instructions for Use).

Revised: 01/2024

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Pulmonary Arterial Hypertension

YUTREPIA is indicated for the treatment of pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability. Studies establishing effectiveness predominately included patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).

The effects diminish over the minimum recommended dosing interval of 4 hours; treatment timing can be adjusted for planned activities.

While there are long-term data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil has been on a background of bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase type 5 inhibitor). The controlled clinical experience was limited to 12 weeks in duration [*see Clinical Studies (14)*].

1.2 Pulmonary Hypertension Associated with ILD

YUTREPIA is indicated for the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability. The study establishing effectiveness predominately included patients with etiologies of idiopathic interstitial pneumonia (IIP) (45%) inclusive of idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE) (25%), and WHO Group 3 connective tissue disease (22%) [*see Clinical Studies (14.2)*].

2 DOSAGE AND ADMINISTRATION

2.1 Usual Dosage In Adults

YUTREPIA capsules are for oral inhalation only and should be used only with the supplied inhaler.

YUTREPIA Dosing in treprostinil-naïve patients:

In patients naïve to treprostinil, therapy should begin with 26.5 mcg 3 to 5 times per day, in 2 breaths based on patient response.

Dosing in patients transitioning from treprostinil inhalation solution (Tyvaso):

Patients transitioning from treprostinil inhalation solution (Tyvaso), can begin YUTREPIA therapy 3 to 5 times per day, in 2 breaths, using the doses specified below (**Error! Reference source not found.**):

Table 1: YUTREPIA Dosing in Patients Transitioning from Treprostinil Inhalation Solution

Current Tyvaso Dose*	YUTREPIA Dose
Breaths	mcg
≤5	26.5

≥ 6 and ≤ 8	53
≥ 9 and ≤ 11	79.5
≥ 12 and ≤ 14	106
≥ 15 and ≤ 17	132.5
≥ 18	159

*Each breath of Tyvaso delivers approximately 6 mcg of treprostinil

In treprostinil-naïve patients and those transitioning from treprostinil inhalation solution, dose increases of 26.5 mcg per dose each week may be implemented, as tolerated. The target maintenance dosage is 79.5-106 mcg, 4 times daily. Doses above 848 mcg per day have not been studied in patients with PAH.

3 DOSAGE FORMS AND STRENGTHS

YUTREPIA inhalation powder contained in capsule available in 4 strengths:

- 26.5 mcg: opaque yellow cap and clear body capsule with “LIQUIDIA 26.5” in black radial imprint on capsule cap.
- 53 mcg: opaque green cap and clear body capsule with “LIQUIDIA 53” in white radial imprint on capsule cap.
- 79.5 mcg: opaque blue cap and clear body capsule with “LIQUIDIA 79.5” in white radial imprint on capsule cap.
- 106 mcg: opaque purple cap and clear body capsule with “LIQUIDIA 106” in white radial imprint on capsule cap.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Symptomatic Hypotension

Treprostinil is a pulmonary and systemic vasodilator. In patients with low systemic arterial pressure, treatment with treprostinil may produce symptomatic hypotension.

5.2 Risk of Bleeding

Treprostinil inhibits platelet aggregation and increases the risk of bleeding.

5.3 Effect of Other Drugs on Treprostinil

Co-administration of a cytochrome P450 (CYP) 2C8 enzyme inhibitor (e.g., gemfibrozil) may increase exposure (both C_{max} and AUC) to treprostinil. Co-administration of a CYP2C8 enzyme inducer (e.g., rifampin) may decrease exposure to treprostinil. Increased exposure is likely to increase adverse events associated with treprostinil administration, whereas decreased exposure is likely to reduce clinical effectiveness [see *Drug Interactions (7.1) and Clinical Pharmacology (12.3)*].

5.4 Bronchospasm

Like other inhaled prostaglandins, YUTREPIA may cause acute bronchospasm. Patients with asthma or chronic obstructive pulmonary disease (COPD), or other bronchial hyperreactivity, are at increased risk for bronchospasm. Ensure that such patients are treated optimally for reactive airway disease prior to and during treatment with YUTREPIA.

6 ADVERSE REACTIONS

The following potential adverse reactions are described in Warnings and Precautions (5):

- Decrease in systemic blood pressure *[see Warnings and Precautions (5.1)]*.
- Bleeding *[see Warnings and Precautions (5.2)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety and tolerability of YUTREPIA was evaluated in an open label study (INSPIRE) of 121 patients with PAH (WHO Group 1 and NYHA Functional Class II [80 patients] and Class III [41 patients]) followed for up to 2 months. The most commonly reported adverse reactions included cough, headache, throat irritation, dizziness, which are known side effects of treprostinil inhalation solution. **Error! Reference source not found.** lists the adverse reactions that occurred at a rate of at least 4% of the overall INSPIRE safety population. The adverse reactions in the INSPIRE study were consistent with those observed in previous studies of inhaled treprostinil.

Error! Reference source not found.: Adverse Reactions Occurring in $\geq 4\%$ of Patients in the INSPIRE Study

Adverse Reaction	Transition* N=55	Add-On† N=66
	n (%)	n (%)
Cough	15 (27)	36 (55)
Headache	14 (25)	18 (27)
Throat Irritation	5 (9)	14 (21)
Dizziness	6 (11)	7 (11)
Diarrhea	3 (6)	8 (12)
Chest Discomfort	5 (9)	5 (8)
Nausea	4 (7)	5 (8)
Dyspnea	3 (6)	3 (5)
Flushing	1 (2)	5 (8)
Oropharyngeal Pain	1 (2)	4 (6)

*Transition: Patients were on stable doses of treprostinil inhalation solution for at least 3 months prior to enrollment in the study and transitioned to treatment with YUTREPIA.

†Add-on: Patients were prostacyclin-naïve and were taking no more than 2 approved oral PAH therapies for at least 3 months at time of enrollment and addition of treatment with YUTREPIA.

6.2 Adverse Reactions Identified in Post-Marketing Experience

The following adverse reaction has been identified during the post-approval use of treprostinil inhalation solution. Because this reaction is reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure:

- Angioedema

7 DRUG INTERACTIONS

7.1 Effect of Cytochrome P450 Inhibitors and Inducers

In vitro studies of human hepatic microsomes showed that treprostinil does not inhibit cytochrome P450 (CYP) isoenzymes CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A.

Additionally, treprostinil does not induce cytochrome P450 isoenzymes CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A.

Human pharmacokinetic studies with an oral formulation of treprostinil (treprostinil diolamine) indicated that co-administration of the cytochrome P450 (CYP) 2C8 enzyme inhibitor gemfibrozil increases exposure (both C_{max} and AUC) to treprostinil. Co-administration of the CYP2C8 enzyme inducer rifampin decreases exposure to treprostinil. It is unclear if the safety and efficacy of treprostinil by the inhalation route are altered by inhibitors or inducers of CYP2C8 [see *Warnings and Precautions* (5.3)].

7.2 Effect of Other Drugs on Treprostinil

Drug interaction studies have been carried out with treprostinil (oral or subcutaneous) co-administered with acetaminophen (4 g/day), warfarin (25 mg/day), and fluconazole (200 mg/day), respectively, in healthy volunteers. These studies did not show a clinically significant effect on the pharmacokinetics of treprostinil. Treprostinil does not affect the pharmacokinetics or pharmacodynamics of warfarin. The pharmacokinetics of R- and S- warfarin and the INR in healthy subjects given a single 25 mg dose of warfarin were unaffected by continuous subcutaneous infusion of treprostinil at an infusion rate of 10 ng/kg/min.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited case reports of treprostinil use in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. However, there are risks to the mother and the fetus associated with pulmonary arterial hypertension (see *Clinical Considerations*). In animal studies, no adverse reproductive and

developmental effects were seen for treprostinil at ≥ 9 and ≥ 145 times the human exposure when based on C_{\max} and AUC, respectively, following a single YUTREPIA dose of 79.5 mcg [see *Clinical Pharmacology* (12.3)].

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and embryo-fetal risk

Pulmonary arterial hypertension is associated with an increased risk of maternal and fetal mortality.

Data

Animal reproduction studies have been conducted with treprostinil via continuous subcutaneous administration and with treprostinil diolamine administered orally. In studies with orally administered treprostinil diolamine, no adverse effect doses for fetal viability/growth, fetal development (teratogenicity), and postnatal development were determined in rats. In pregnant rats, no evidence of harm to the fetus was observed following oral administration of treprostinil diolamine at the highest dose tested (20 mg/kg/day), which represents about 154 and 1479 times the human exposure, when based on C_{\max} and AUC, respectively, following a single YUTREPIA dose of 79.5 mcg. In pregnant rabbits, external fetal and soft tissue malformations and fetal skeletal malformation occurred. The dose at which no adverse effects were seen (0.5 mg/kg/day) represents about 9 and 145 times the human exposure, when based on C_{\max} and AUC, respectively, following a single YUTREPIA dose of 79.5 mcg. No treprostinil treatment-related effects on labor and delivery were seen in animal studies. Animal reproduction studies are not always predictive of human response.

8.2 Lactation

Risk Summary

There are no data on the presence of treprostinil in human milk, the effects on the breastfed infant, or the effects on milk production.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Placebo-controlled clinical studies of treprostinil inhalation solution did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. The open-label INSPIRE study in PAH patients included 28 patients aged 65 and over in which no age-related differences were noted. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of hepatic, renal, or cardiac dysfunction, and of concomitant diseases or other drug therapy.

8.6 Patients with Hepatic Insufficiency

Plasma clearance of treprostinil, delivered subcutaneously, was reduced up to 80% in subjects with mild-to-moderate hepatic insufficiency. Uptitrate slowly when treating patients with hepatic insufficiency because of the risk of an increase in systemic exposure which may lead to an increase in dose-dependent adverse effects. Treprostinil has not been studied in patients with severe hepatic insufficiency [see *Clinical Pharmacology* (12.3)].

8.7 Patients with Renal Insufficiency

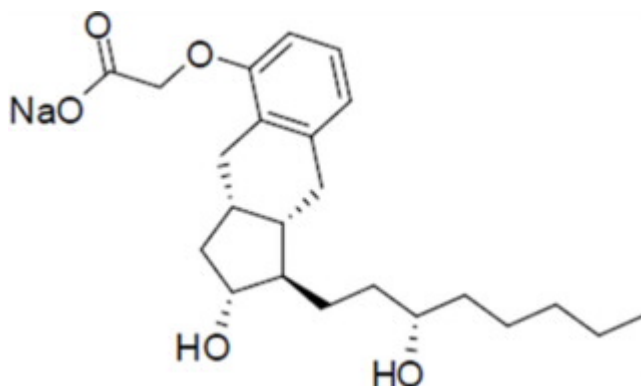
No dose adjustments are required in patients with renal impairment. Treprostinil is not cleared by dialysis [see *Clinical Pharmacology* (12.3)].

10 OVERDOSAGE

In general, symptoms of overdose with treprostinil include flushing, headache, hypotension, nausea, vomiting, and diarrhea. Provide general supportive care until the symptoms of overdose have resolved.

11 DESCRIPTION

YUTREPIA contains treprostinil sodium, a prostacyclin vasodilator. The chemical name for treprostinil sodium is 2-{[(1R,2R,3aS,9aS)-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H,2H,3H,3aH,4H,9H,9aH-cyclopenta[b]naphthalen-5-yl]oxy}acetic acid, sodium salt with the structural formula:



Treprostinil sodium has a molecular formula of $C_{23}H_{33}O_5Na$ and a molecular weight of 412.49 daltons equivalent to 390.5 daltons of Treprostinil

YUTREPIA inhalation powder contained in a capsule is intended for oral inhalation. The capsule contains white to off-white powder of treprostinil sodium and the inactive ingredients trehalose, polysorbate 80, L-leucine, sodium citrate, and sodium chloride. 26.5 mcg of treprostinil is equivalent to 28 mcg of treprostinil sodium.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The major pharmacologic actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation.

12.2 Pharmacodynamics

In animals, the vasodilatory effects reduce right and left ventricular afterload and increase cardiac output and stroke volume. Other studies have shown that treprostinil causes a dose-related negative inotropic and lusitropic effect. No major effects on cardiac conduction have been observed. Treprostinil produces vasodilation and tachycardia.

Cardiac Electrophysiology

In a clinical trial of 240 healthy volunteers, single doses of treprostinil inhalation solution 54 mcg (the target maintenance dose per session) and 84 mcg (supratherapeutic inhalation dose) prolonged the corrected QTc interval by approximately 10 ms. The QTc effect dissipated rapidly as the concentration of treprostinil decreased.

12.3 Pharmacokinetics

Absorption

in healthy volunteer studies, the systemic exposure (AUC and C_{max}) post-inhalation was shown to be proportional to the YUTREPIA doses administered (25 mcg – 150 mcg). The treprostinil mean C_{max} , mean AUC_{inf} and median T_{max} following a single inhaled target maintenance dose of 79.5 mcg YUTREPIA were 1.48 ng/mL, 1.04 hr.ng/mL and 0.13 hr, respectively.

Distribution

In vitro treprostinil is 91% bound to human plasma proteins over the 330-10,000 ng/mL concentration range.

Metabolism and Excretion

Of subcutaneously administered treprostinil, only 4% is excreted unchanged in urine. Treprostinil is substantially metabolized by the liver, primarily by CYP2C8. Metabolites are excreted in urine (79%) and feces (13%) over 10 days. Five apparently inactive metabolites were detected in the urine, each accounting for 10-15% of the dose administered. Four of the metabolites are products of oxidation of the 3-hydroxyoctyl side chain and one is a glucuroconjugated derivative (treprostinil glucuronide).

Elimination

Following inhaled administration of YUTREPIA, disposition and elimination is monophasic with a half-life of approximately 30 minutes.

Specific Populations

Hepatic Insufficiency

Plasma clearance of treprostinil, delivered subcutaneously, was reduced up to 80% in subjects presenting with mild-to-moderate hepatic insufficiency. Treprostinil has not been studied in patients with severe hepatic insufficiency [see *Use in Specific Populations* (8.6)].

Renal Insufficiency

In patients with severe renal impairment requiring dialysis (n=8), administration of a single 1 mg dose of orally administered treprostinil pre-and post-dialysis resulted in AUC_{0-inf} that was not significantly altered compared to healthy subjects [see *Use in Specific Populations* (8.7)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

A two-year rat carcinogenicity study was performed with treprostinil inhalation solution at target treprostinil doses of 5.26, 10.6, and 34.1 µg/kg/day. There was no evidence for carcinogenic potential associated with treprostinil inhalation in rats at systemic exposure levels up to 35 times following a single YUTREPIA dose of 79.5 mcg [see *Clinical Pharmacology* (12.3)]. *In vitro* and *in vivo* genetic toxicology studies did not demonstrate any mutagenic or clastogenic effects of treprostinil. Treprostinil sodium did not affect fertility or mating performance of male or female rats given continuous subcutaneous (sc) infusions at rates of up to 450 ng treprostinil/kg/min. In this study, males were dosed from 10 weeks prior to mating and through the 2-week mating period. Females were dosed from 2 weeks prior to mating until gestational day 6.

Oral administration of treprostinil diolamine to Tg.rasH2 mice at 0, 5, 10 and 20 mg/kg/day in males and 0, 3, 7.5 and 15 mg/kg/day in females daily for 26 weeks did not significantly increase the incidence of tumors.

Treprostinil diolamine was tested *in vivo* in a rat micronucleus assay and did not induce an increased incidence of micronucleated polychromatic erythrocytes.

13.2 Animal Toxicology and/or Pharmacology

In a 2-year rat study with treprostinil inhalation at target doses of 5.26, 10.6, and 34.1 mcg/kg/day, there were more deaths (11) in the mid- and high-dose treprostinil groups during the first 9 weeks of the study, compared to 1 in control groups. At the high-dose level, males showed a higher incidence of inflammation in teeth and preputial gland, and females showed high incidences of inflammation and urothelial hyperplasia in the urinary bladder. The exposures in rats at mid- and high-dose levels were about 15 and 35 times, respectively, the clinical exposure following a single YUTREPIA dose of 79.5 mcg [see *Clinical Pharmacology* (12.3)].

14 CLINICAL STUDIES

14.1 Pulmonary Arterial Hypertension (WHO Group 1)

TRIUMPH I was a 12-week, randomized, double-blind, placebo-controlled multi-center study of patients with PAH. The study population included 235 clinically stable patients with pulmonary arterial hypertension (WHO Group 1), nearly all with NYHA Class III (98%) symptoms who were receiving either bosentan (an endothelin

receptor antagonist) or sildenafil (a phosphodiesterase-5 inhibitor) for at least three months prior to study initiation. Concomitant therapy also could have included anticoagulants, other vasodilators (e.g., calcium channel blockers), diuretics, oxygen, and digitalis, but not a prostacyclin. These patients were administered either placebo or treprostinil inhalation solution in four daily treatment sessions with a target dose of 9 breaths (equivalent to 79.5 mcg YUTREPIA) per session over the course of the 12-week study. Patients were predominantly female (82%), had the origin of PAH as idiopathic/heritable (56%), secondary to connective tissue diseases (33%) or secondary to HIV or previous use of anorexigens (12%); bosentan was the concomitant oral medication in 70% of those enrolled, sildenafil in 30%.

The primary efficacy endpoint of the trial was the change in six-minute walk distance (6MWD) relative to baseline at 12 weeks. 6MWD was measured at peak exposure (between 10 and 60 minutes after dosing), and 3-5 hours after bosentan or 0.5-2 hours after sildenafil. Patients receiving treprostinil inhalation solution had a placebo-corrected median change from baseline in peak 6MWD of 20 meters at Week 12 ($p < 0.001$).

The distribution of these 6MWD changes from baseline at Week 12 were plotted across the range of observed values (Figure 11). 6MWD measured at trough exposure (defined as measurement of 6MWD at least 4 hours after dosing) improved by 14 meters. There were no placebo-controlled 6MWD assessments made after 12 weeks.

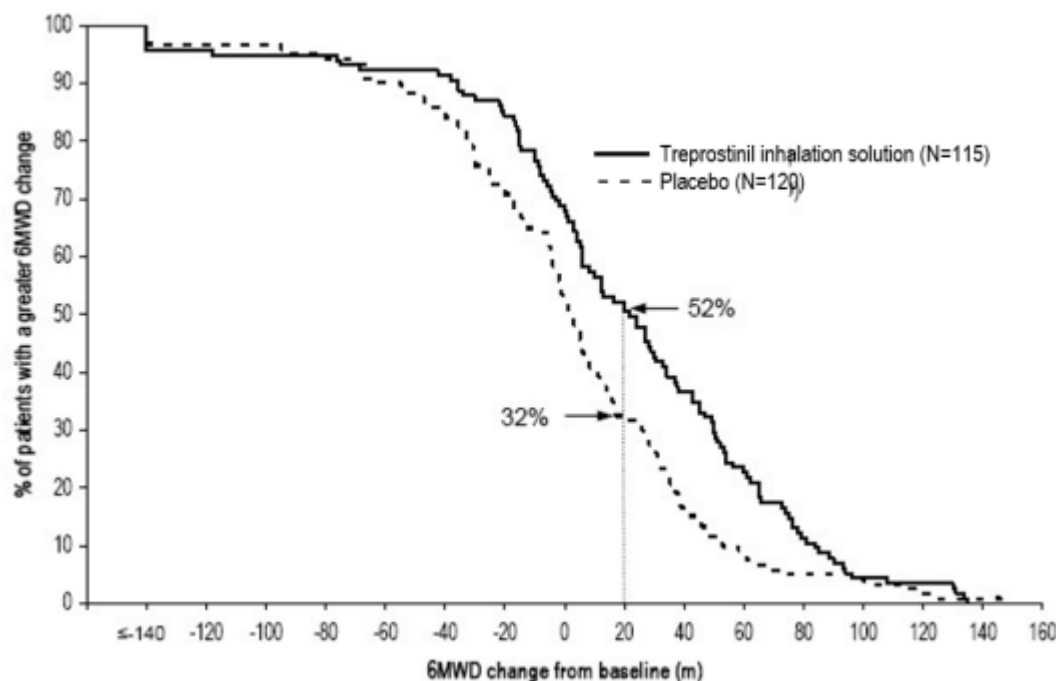


Figure 1. Distributions of 6MWD Changes from Baseline at Week 12 during Peak Plasma Concentration of Treprostinil Inhalation Solution

The placebo-corrected median treatment effect on 6MWD was estimated (using the Hodges-Lehmann estimator) within various subpopulations defined by age quartile, gender, geographic region of the study site, disease etiology, baseline 6MWD quartile, and type of background therapy (Figure 2).

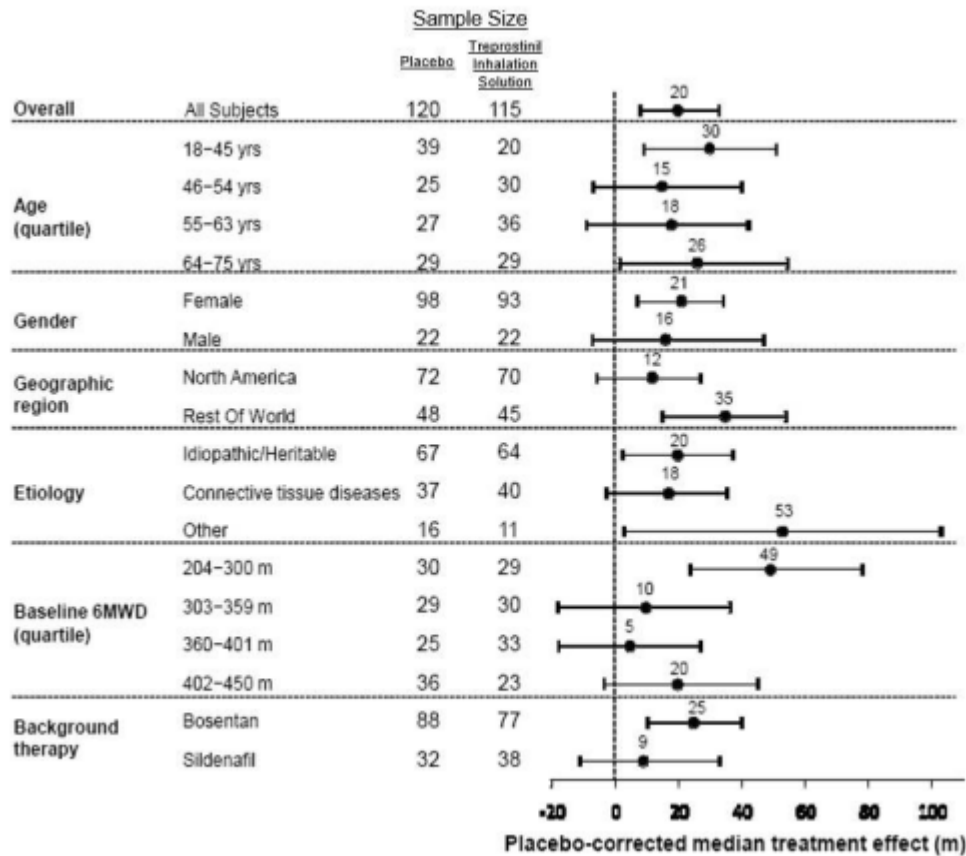


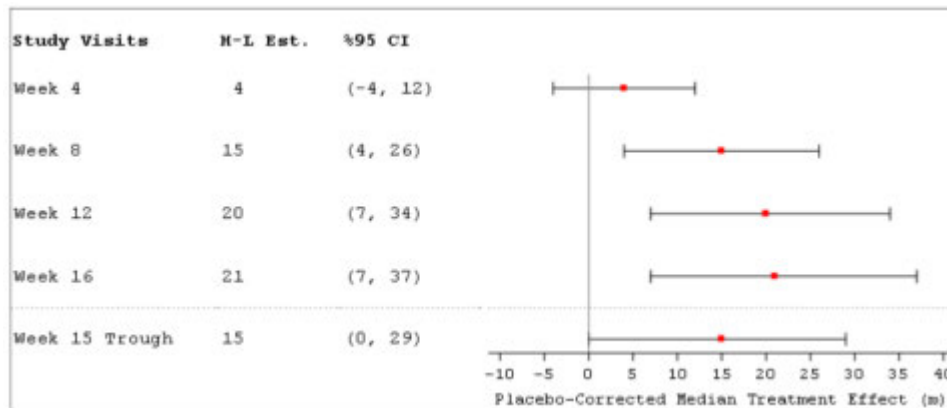
Figure 2. Placebo-Corrected Median Treatment Effect (Hodges-Lehmann estimate with 95% CI) on 6MWD Change from Baseline at Week 12 During Peak Plasma Concentration of Treprostinil Inhalation Solution for Various Subgroups

14.2 Pulmonary Hypertension Associated with ILD (WHO Group 3)

INCREASE was a 16-week, randomized, double-blind, placebo-controlled, multicenter study that enrolled 326 patients with PH-ILD. Enrolled study patients predominately had etiologies of idiopathic interstitial pneumonia (45%) inclusive of idiopathic pulmonary fibrosis, combined pulmonary fibrosis and emphysema (25%), and WHO Group 3 connective tissue disease (22%). The mean baseline 6MWD was 260 meters.

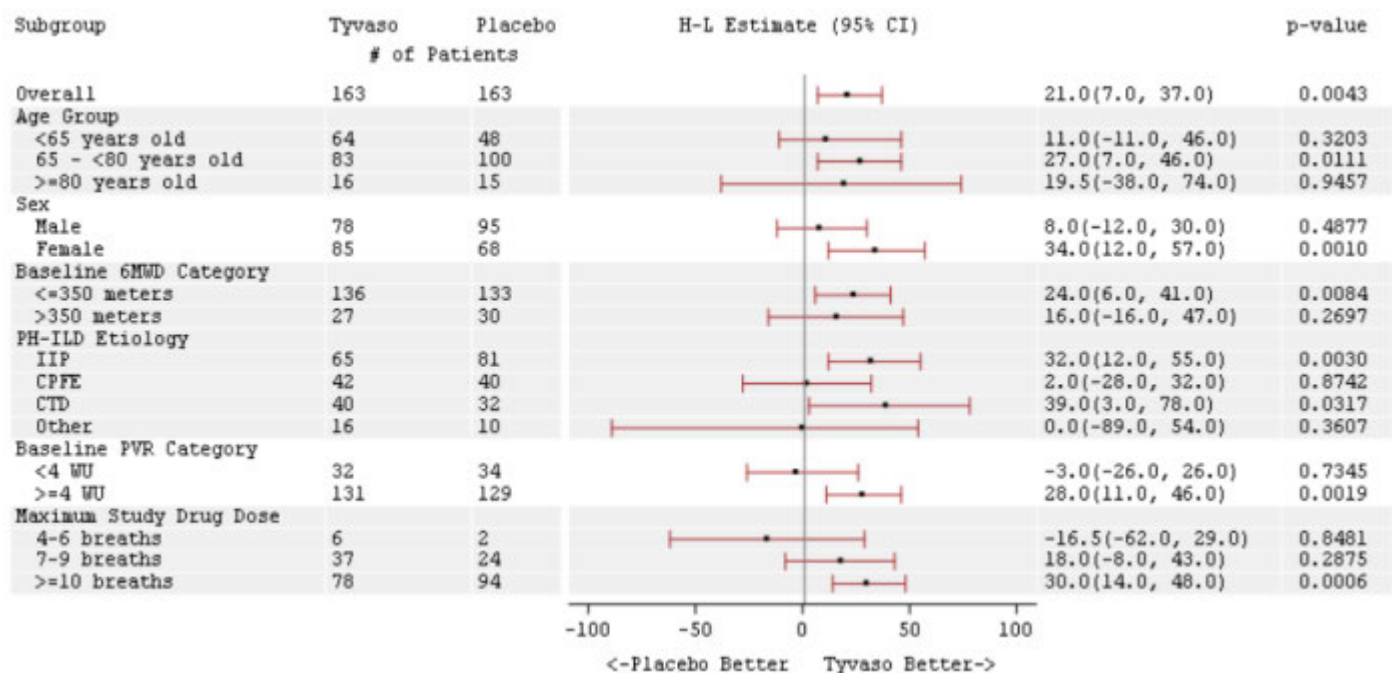
Patients in the INCREASE study were randomized (1:1) to either placebo or treprostinil inhalation solution in four daily treatment sessions with a target dose of 9 breaths (equivalent to 79.5 mcg YUTREPIA) per session and a maximum dose of 12 breaths (equivalent to 106 mcg YUTREPIA) per session over the course of the 16-week study. Approximately 75% of patients randomized to treprostinil inhalation solution titrated up to a dose of 9 breaths, 4 times daily or greater, with 48% of patients randomized to treprostinil inhalation solution reaching a dose of 12 breaths, 4 times daily during the study. The primary efficacy endpoint was the change in 6MWD measured at peak exposure (between 10 and 60 minutes after dosing) from baseline to Week 16. Patients receiving treprostinil inhalation solution had a placebo-corrected median change from baseline in peak 6MWD of 21 meters at Week 16 ($p=0.004$) using Hodges-Lehmann estimate (Figure 3).

Figure 3: Hodges-Lehmann Estimate of Treatment Effect by Visit for 6MWD at Peak Exposure (PH-ILD)



The treatment effect on 6MWD at Week 16 was consistent for various subgroups, including etiology of PH-ILD, disease severity, age, sex, baseline hemodynamics, and dose (Figure 4).

Figure 4: Forest Plot on Subgroup Analyses of Peak 6MWD (Meter) at Week 16 (PH-ILD)



Time to clinical worsening in the INCREASE study was defined as the time of randomization until 1 of the following criteria were met: hospitalization due to a cardiopulmonary indication, decrease in 6MWD >15% from baseline directly related to PH-ILD at 2 consecutive visits and at least 24 hours apart, death (all causes), or lung transplantation. Treatment with treprostinil inhalation solution in patients with PH-ILD resulted in numerically fewer hospitalizations. The numbers of reported deaths were the same for both treatment groups (Table 3). Overall, treatment with treprostinil inhalation solution demonstrated a statistically significant

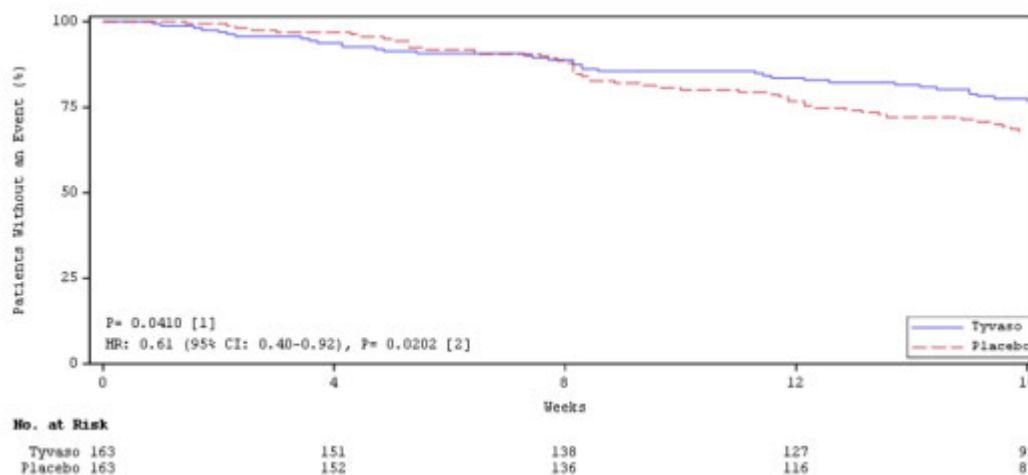
increase in the time to first clinical worsening event (log-rank test $p=0.041$; Figure 5), and a 39% overall reduction in the risk of a clinical worsening event ($HR=0.61$ [95% CI: 0.40, 0.92]; Figure 5).

Error! Reference source not found: Clinical Worsening Events (PH-ILD)

		Tyvaso n=163 n (%)	Placebo n=163 n (%)	HR (95% CI)
Clinical worsening		37 (22.7%)	54 (33.1%)	0.61 (0.40, 0.92)
First contributing event	Hospitalization due to a cardiopulmonary indication	18 (11.0%)	24 (14.7%)	
	Decrease in 6MWD >15% from baseline directly related to PH-ILD	13 (8.0%)	26 (16.0%)	
	Death (all causes)	4 (2.5%)	4 (2.5%)	
	Lung transplantation	2 (1.2%)	0	

		Tyvaso n=163 n (%)	Placebo n=163 n (%)	HR (95% CI)
First of each event	Hospitalization due to a cardiopulmonary indication	21 (12.9)	30 (18.4%)	
	Decrease in 6MWD >15% from baseline directly related to PH-ILD	16 (9.8%)	31 (19.0%)	
	Death (all causes)	8 (4.9%)	10 (6.1%)	
	Lung transplantation	2 (1.2%)	1 (0.6%)	

Figure 5: Kaplan-Meier Plot of Time to Clinical Worsening Events (PH-ILD)



16 HOW SUPPLIED/STORAGE AND HANDLING

YUTREPIA is supplied in a carton consisting of 1 capsule based, dry powder inhaler (referred to as “inhaler”), 28 capsules (7 foil blister cards of 4 capsules each), and 7 single-use cleaning brushes. The individual capsule well is connected by an air channel to a separate blister well containing a desiccant strip. Descriptions of YUTREPIA carton by capsule strength are provided in Table 4 below:

Table 4: YUTREPIA Carton Contents by Capsule Strength

Capsule Strength (mcg treprostinil)	Capsule Description	NDC Number
26.5	Opaque yellow cap, clear body, imprinted with “LIQUIDIA 26.5” in black ink radially on cap	72964-011-01
53	Opaque green cap, clear body, imprinted with “LIQUIDIA 53” in white ink radially on cap	72964-012-01
79.5	Opaque blue cap, clear body, imprinted with “LIQUIDIA 79.5” in white ink radially on cap	72964-013-01
106	Opaque purple cap, clear body, imprinted with “LIQUIDIA 106” in white ink radially on cap	72964-014-01

YUTREPIA inhalation powder capsules should only be delivered using the capsule-based inhaler.. The off-white plastic inhaler consists of a blue protective cap marked with YUTREPIA and a base with a mouthpiece, capsule chamber, and two blue push buttons. Discard the inhaler device after 7 days of use or 56 actuations, whichever comes first.

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Capsules should remain in the blister to protect them from moisture and light, and each capsule should be removed only when ready to administer a dose.

Keep out of the reach of children.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Instructions for Use).

Train patients in the administration process for YUTREPIA, including dosing, inhaler preparation, administration, cleaning, and maintenance, according to the instructions for use [see *Instructions for Use*].

To avoid potential interruptions in drug delivery because of equipment malfunction, patients should have access to a back-up.

In the event that a scheduled dose is missed, take another dose as soon as possible.

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EXHIBIT 9

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS,)
)
Plaintiff,)
) C.A. No. 23-975-RGA
v.)
)
LIQUIDIA TECHNOLOGIES,)
)
Defendant.)

J. Caleb Boggs Courthouse
844 North King Street
Wilmington, Delaware

Tuesday, April 23, 2024
3:00 p.m.
Oral Argument

BEFORE: THE HONORABLE RICHARD G. ANDREWS, U.S.D.C.J.

APPEARANCES:

MORRIS NICHOLS ARSHT & TUNNELL LLP
BY: MICHAEL J. FLYNN, ESQUIRE

-and-

McDERMOTT WILL & EMERY LLP
BY: DOUGLAS CARSTEN, ESQUIRE
BY: ADAM BURROWBRIDGE, ESQUIRE
BY: ART DYKHUIS, ESQUIRE
BY: WILLIAM JACKSON, ESQUIRE
BY: KATHERINE CHENG, ESQUIRE
BY: ERIC ROMEO, ESQUIRE

For the Plaintiff

1 APPEARANCES CONTINUED:

2 SHAW KELLER LLP
3 BY: KAREN E. KELLER, ESQUIRE

4 -and-

5 COOLEY LLP
6 BY: SANYA SUKDUANG, ESQUIRE
BY: JOHN HABIBI, ESQUIRE
BY: PHILLIP MORTON, ESQUIRE

02:42:04 7 For the Defendant

02:42:04

02:51:42 8 *** PROCEEDINGS ***

02:51:42 9 DEPUTY CLERK: All rise. Court is now in
02:51:59 10 session. The Honorable Richard G. Andrews presiding.

02:55:03 11 THE COURT: All right. Please be seated.

03:00:06 12 This is the time set for argument on the motion
03:00:10 13 for preliminary injunction by United Therapeutics in the
03:00:15 14 case against Liquidia, Number 23-975.

03:00:22 15 MR. CARSTEN: Yes, Your Honor.

03:00:25 16 THE COURT: Yeah. I'm looking for Mr. Flynn.
03:00:28 17 There he is.

03:00:28 18 MR. FLYNN: I'm here, Your Honor.

03:00:29 19 THE COURT: So do you want to introduce any of
03:00:31 20 these people?

03:00:32 21 MR. FLYNN: I'd be happy to, Your Honor.

03:00:34 22 Good afternoon, Michael Flynn from Morris

03:00:39 23 Nichols on behalf of United Therapeutics Corporation.

03:00:44 24 Seated at counsel table are Doug Carsten from McDermott Will
03:00:46 25 & Emery, William Jackson from Goodwin Procter, and Shaun

03:55:40 1 presented anybody from UTC in declaration form to say, This
03:55:44 2 is what's going to happen.

03:55:45 3 And, in fact, when you look at Dr. Selck's
03:55:48 4 testimony, and we had it, I believe, on Slide 2. When
03:55:52 5 asked, Has UTC actually done anything in response to payors'
03:55:57 6 requests? Dr. Selck was -- I asked UTC that, and UTC
03:56:02 7 doesn't -- you don't need to move the slides. UTC indicated
03:56:06 8 that they have not made a decision yet.

03:56:09 9 So, in addition to establishing a nexus,
03:56:11 10 irreparable harm cannot be speculative. You heard from
03:56:14 11 Mr. Carsten today that they're trying to look at a crystal
03:56:17 12 ball. You can't find irreparable harm based on speculation.

03:56:20 13 THE COURT: Well, so help me just a bit. You
03:56:25 14 said that UTC had made a decision a moment ago. Is this the
03:56:37 15 kind of thing that PH-ILD, they don't know whether you're
03:56:42 16 going to be on the market or not for ILD, that they start
03:56:49 17 cutting their prices on the premise that you might be on the
03:56:52 18 market?

03:56:52 19 MR. SUKDUANG: No, that's not the way
03:56:54 20 formularies work. The way formularies work, as you enter a
03:56:57 21 contract with the payors to get on the formulary, you
03:57:01 22 negotiate that contract ahead of time. That's the
03:57:04 23 conversations that Mr. Barton apparently had been having
03:57:07 24 with these payors. It's the contract negotiation.

03:57:11 25 UTC has to decide, Okay, their 2023 forecast

03:57:16 1 assumes our launch in 2024. They go with that information
03:57:22 2 to the payors. UTC now provides some nominal discount to
03:57:26 3 payors, maybe five percent on their pricing. They need to
03:57:30 4 decide: Are we actually going to chase the price? Or the
03:57:34 5 other tack that companies can do is we're going to keep our
03:57:38 6 price the same, because, as Dr. Rothblatt has said, we're a
03:57:44 7 branded product, and we're strongly differentiated.

03:57:48 8 So companies can keep pricing the way they are.
03:57:50 9 And what they do is say, Don't use YUTREPIA, use ours
03:57:54 10 because of A, B and C. We're better. If they believe their
03:57:58 11 device is better, our device is better. Your patient has
03:58:01 12 been on our drug, whether it's the nebulizer, or Remodulin
03:58:05 13 or DPI for the past 20 years. They're doing well. Don't
03:58:09 14 change now.

03:58:09 15 So this first-mover advantage that UTC says it's
03:58:14 16 going to be eroded doesn't get eroded. They don't need to
03:58:17 17 change their pricing to impact or to compete with YUTREPIA.

03:58:22 18 The other part that Mr. Carsten said was, based
03:58:26 19 on these conversations, YUTREPIA is going to be at some
03:58:32 20 major discount to TYVASO. Where is that? There's no
03:58:37 21 documentation to that. Mr. Barton didn't testify to that.
03:58:41 22 And we have -- Dr. Selck didn't take any notes.

03:58:44 23 It's just Dr. Selck saying, without any support,
03:58:48 24 that, Oh, TYVASO is going to be at 20, or 30 or 40 percent
03:58:53 25 discount. Excuse me, YUTREPIA is going to be at some major

03:58:57 1 discount to TYVASO.

03:58:58 2 There's no evidence of that. Because what
03:59:00 3 Liquidia can do is match price with TYVASO. So this idea
03:59:06 4 that there's going to be price erosion is speculative. The
03:59:11 5 case that Mr. Carsten cited, the *Sanofi* case, one of them is
03:59:16 6 a generic case. And as Your Honor knows, once a generic
03:59:20 7 comes on the market, yes, the branded price --

03:59:23 8 THE COURT: Generics are different.

03:59:24 9 MR. SUKDUANG: -- goes down. It's different.

03:59:25 10 The other case is the -- I think he called it
03:59:27 11 the *Glaxo vs. Kali* case. And this goes to the validity.
03:59:33 12 That case is different because that dealt with migraines,
03:59:36 13 and not every migraine patient had nausea. That's why there
03:59:39 14 was no anticipation.

03:59:41 15 The '793 patent is different. Every PH patient,
03:59:44 16 whether it's PAH or PH-ILD, because of the nature of their
03:59:48 17 disease, has impaired exercise capacity. And, in fact, when
03:59:52 18 you look at the labels, and I pointed this out earlier --
03:59:55 19 when you look at the labels, on the left-hand side is the
04:00:01 20 TYVASO label. And on the right-hand side is the proposed
04:00:05 21 YUTREPIA label.

04:00:06 22 PAH is not treating PAH. It's treating the PAH
04:00:12 23 to improve exercise ability.

04:00:14 24 For ILD, it's pulmonary hypertension associated
04:00:18 25 with interstitial lung disease. But as Dr. Nathan

04:00:22 1 testified, interstitial lung disease is -- the ILD is not
04:00:25 2 being treated by Treprostinil. It doesn't work for that.
04:00:28 3 It works on the hypertension part, to improve exercise
04:00:32 4 capacity.

04:00:32 5 So when you look at the '793 patent, and I'm
04:00:34 6 moving to validity, Your Honor, if I wasn't clear. When you
04:00:37 7 look at the '793 patent, we don't have a *Glaxo vs. Kali*
04:00:42 8 issue here, because whether you have PAH or you have PH-ILD,
04:00:49 9 the problem is the same. It's exercise capacity.

04:00:53 10 Now, the patient population with respect to the
04:00:56 11 '793, UTC argues that they're different. It's not
04:01:00 12 different. The '793 disclosure is directed to pulmonary
04:01:04 13 hypertension. Pulmonary hypertension is all five groups.
04:01:08 14 Pulmonary hypertension ILD is Group 3.

04:01:12 15 If you look at Table 3, and Table 3 is
04:01:15 16 associated with Example 2 of the '793 patent. In every
04:01:19 17 single study, Study 1, Study 2 or Study 3 in Example 2,
04:01:26 18 PH-ILD patients were present.

04:01:29 19 There is no dispute that the '793 discloses
04:01:33 20 teaching PH-ILD patients. Dr. Nathan admits that.

04:01:37 21 With respect to dosing, UTC argued today that
04:01:42 22 the dosing is different. It's not. When you look at the
04:01:45 23 studies, again, I'm pointing to Example 2, the '327 patent
04:01:50 24 claim requires at least 15 micrograms of Treprostinil and at
04:01:55 25 least six micrograms per breath.

04:01:58 1 Okay. The '793 patent discloses in the
04:02:02 2 specification generally 15 to 90 micrograms, and you can use
04:02:07 3 a number of breaths. One to three is the exemplary. But
04:02:11 4 when you look at the examples themselves.

04:02:13 5 Example 2 there was a single breath at
04:02:18 6 30 micrograms. That meets Claim 1 of the '327 patent.

04:02:22 7 Study 3 looked at 15 micrograms at a number of
04:02:27 8 different doses. One breath, two breaths or three breaths.
04:02:30 9 One breath and two breaths meet the six-microgram dose.
04:02:33 10 Excuse me, at least six micrograms per breath. The '793
04:02:37 11 patent discloses the exact same dosing.

04:02:41 12 With respect to -- and Your Honor made a comment
04:02:44 13 about our infringement versus our validity. These are all
04:02:47 14 Claim 1.

04:02:48 15 Our invalidity positions target every single
04:02:51 16 claim. We don't believe one being stronger or weaker than
04:02:55 17 the other. Claim 1 is clearly anticipated either expressly
04:02:58 18 or inherently.

04:02:59 19 Claim 11 and 14, these are the device claims.
04:03:04 20 Pulse inhalation device or dry powder inhaler. There's no
04:03:06 21 dispute that the '793 patent discloses both. We had two
04:03:09 22 days of trial testimony regarding the devices in the prior
04:03:12 23 case.

04:03:12 24 The real issue that UTC presents is this
04:03:16 25 exercise capacity. When you look at the '793 patent, it

04:03:19 1 discloses the hemodynamic data. This '793 patent was used
04:03:27 2 to enjoin us on an indication, not for PAH. It was used to
04:03:31 3 enjoin us on an indication for PAH to improve exercise
04:03:36 4 capacity. That was the label that we had that Your Honor
04:03:42 5 priorly addressed.

04:03:43 6 The data in the '793 patent we acknowledge is
04:03:46 7 hemodynamic data. That hemodynamic data shows the
04:03:50 8 functional change.

04:03:51 9 How do we know that? In the prior case,
04:03:54 10 Dr. Clark and Dr. Waxman testified that when you look at in
04:03:58 11 terms of these hemodynamic pressures in the '793 patent,
04:04:03 12 yes, it has a therapeutic benefit because of hemodynamic
04:04:06 13 data.

04:04:07 14 ANSWER: Correct. Yeah.

04:04:08 15 And also your opinion that a drug is
04:04:11 16 therapeutically effective if it benefits a patient's
04:04:12 17 exercise ability?

04:04:14 18 ANSWER: In the long term, yes.

04:04:17 19 The '793 patent, while it discloses hemodynamic
04:04:22 20 data, covers an indication that is not hemodynamic data. It
04:04:29 21 covers an indication in the TYVASO label, and it was used to
04:04:33 22 block our YUTREPIA label for exercise ability and exercise
04:04:37 23 ability only.

04:04:38 24 That's this, the Orange Book on the '793. Don't
04:04:45 25 be fooled. It's exercise ability based on the hemodynamic

04:04:50 1 data.

04:04:51 2 UTC has admitted this. At the bottom slide,
04:04:55 3 they told the FDA in March -- in February. They got a new
04:05:00 4 indication, the PH-ILD indication. And this is leading up
04:05:04 5 to the attempts that led to the D.C. District Court case.

04:05:09 6 They tried to block us at the FDA directly, and
04:05:11 7 the FDA said, No. But they sent a letter -- UTC's counsel
04:05:15 8 sent a letter in February of 2024. They told the FDA that
04:05:19 9 the new indication for TYVASO is treatment of pulmonary
04:05:23 10 hypertension associated with ILD to improve exercise
04:05:27 11 capacity.

04:05:27 12 Then the very next sentence they said, "We sued
04:05:31 13 Liquidia timely for patent infringement, but the litigation
04:05:36 14 didn't have the 30-month stay." But they said "on the
04:05:39 15 patents covering the new indication, the '793 patent."
04:05:44 16 They're telling the FDA that the '793 patent covers this new
04:05:49 17 indication which is only exercise capacity.

04:05:52 18 THE COURT: But you could have two patents cover
04:05:54 19 an indication, and that doesn't mean that they each
04:05:57 20 anticipate each other.

04:05:58 21 MR. SUKDUANG: You can have two patents covering
04:06:01 22 the same indication, and they don't anticipate each other.
04:06:03 23 But then in this instance, the '793 patent, when you look at
04:06:07 24 the disclosure, you look at the patient population, it's the
04:06:10 25 same. You look at the dosing, it's the same. You look at

05:00:15 1 Otherwise, you'd just be arguing that the prior
05:00:18 2 art reference anticipates. You don't need to do that for
05:00:23 3 inherency. The '793 anticipates. The INCREASE study
05:00:26 4 demonstrates that inherent property.

05:00:28 5 That was the only point I wanted to make.

05:00:30 6 THE COURT: All right. Well, thank you.

05:00:32 7 All right. Well, I'll look forward to your
05:00:35 8 submissions on Friday. And, you know, if things happen in
05:00:44 9 the outside world with the FDA or even the District Court in
05:00:48 10 the District of Columbia that impacts what we're doing here,
05:00:53 11 please let me know as soon as possible. But, otherwise, I
05:00:59 12 expect we'll put something in writing and we'll try to do it
05:01:05 13 in a relatively prompt fashion.

05:01:07 14 Okay? So thank you for your time today. Thank
05:01:09 15 you for your presentations.

05:01:11 16 DEPUTY CLERK: All rise.

05:01:15 17 ALL COUNSEL: Thank you, Your Honor.

18 (Court was recessed at 5:01 p.m.)

19 I hereby certify the foregoing is a true and
20 accurate transcript from my stenographic notes in the
21 proceeding.

22 /s/ Heather M. Triozzi
23 Certified Merit and Real-Time Reporter
24 U.S. District Court
25

EXHIBIT 10

Clinical perspectives with long-term pulsed inhaled nitric oxide for the treatment of pulmonary arterial hypertension

Robyn J. Barst¹, Richard Channick², Dunbar Ivy³, and Brahm Goldstein⁴

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ABSTRACT

Pulmonary arterial hypertension (PAH) is a chronic, progressive disease of the pulmonary vasculature with a high morbidity and mortality. Its pathobiology involves at least three interacting pathways – prostacyclin (PGI₂), endothelin, and nitric oxide (NO). Current treatments target these three pathways utilizing PGI₂ and its analogs, endothelin receptor antagonists, and phosphodiesterase type-5 (PDE-5) inhibitors. Inhaled nitric oxide (iNO) is approved for the treatment of hypoxic respiratory failure associated with pulmonary hypertension in term/near-term neonates. As a selective pulmonary vasodilator, iNO can acutely decrease pulmonary artery pressure and pulmonary vascular resistance without affecting cardiac index or systemic vascular resistance. In addition to delivery via the endotracheal tube, iNO can also be administered as continuous inhalation via a facemask or a pulsed nasal delivery. Consistent with a deficiency in endogenously produced NO, long-term pulsed iNO dosing appears to favorably affect hemodynamics in PAH patients, observations that appear to correlate with benefit in uncontrolled settings. Clinical studies and case reports involving patients receiving long-term continuous pulsed iNO have shown minimal risk in terms of adverse events, changes in methemoglobin levels, and detectable exhaled or ambient NO or NO₂. Advances in gas delivery technology and strategies to optimize iNO dosing may enable broad-scale application to long-term treatment of chronic diseases such as PAH.

Key Words: drug, hypertension, inhalation administration, nitric oxide, pulmonary arterial hypertension, pulmonary circulation, pulmonary hypertension, pulmonary/physiopathology, pulse therapy, vasodilator agents

Pulmonary arterial hypertension (PAH) is a chronic, progressive disease of the pulmonary vasculature resulting in right ventricular failure and death, if untreated.^[1,2] PAH is defined by the following: a resting mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg; pulmonary capillary wedge pressure or left ventricular end diastolic pressure ≤ 15 mmHg; and pulmonary vascular resistance (PVR) ≥ 3 Wood units.^[2] PAH can be idiopathic, heritable, or associated with other conditions, such as connective tissue diseases (CTDs).^[3,4]

The prevalence of PAH was estimated as 26–52 cases per million from the Scottish epidemiological study; a more conservative lower-bound estimate from the French PAH Registry reports 5–25 cases per million.^[5,6] Prevalence is greater in high-risk groups, such as patients with CTDs, congenital heart disease (repaired and unrepaired), human immunodeficiency virus, and portal hypertension.^[7–9]


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Pulmonary arterial hypertension: Mortality and unmet medical need

The mortality with PAH remains high despite treatment advances over the past several decades. In the 1980s, the 5-year survival rate for idiopathic PAH (IPAH; formerly termed “primary pulmonary hypertension”) was 34% in the National Institutes of Health (NIH) Registry; although 5-year survival has increased to $\approx 60\%$ using currently available drugs, the mortality remains unacceptable.^[4] Patients in the NIH registry in the 1980s were treated with the conventional therapy available at the time, including diuretics, digoxin, supplemental oxygen, warfarin, and

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calcium channel blockers (if clinically indicated).^[4] Prior to 1995, no drugs were approved for PAH. However, there are currently eight drugs approved for the treatment of PAH: intravenous (IV) epoprostenol, IV/subcutaneous (SC) treprostinil, inhaled treprostinil, inhaled iloprost, oral bosentan, oral ambrisentan, oral sildenafil, and oral tadalafil. A meta-analysis of all randomized, controlled PAH trials published through 2008 suggested that with these available PAH-specific treatments, mortality has decreased 43% (RR: 0.57; 95% CI: 0.35–0.92; $P=0.023$).^[10] Despite these improvements in survival rates, a significant unmet medical need remains: PAH continues to progress with no cure.

Patients with PAH also report severe impairment of health-related quality of life (HRQOL), including poor general and emotional health, and impaired physical functioning.^[9] These impairments to HRQOL with PAH are comparable and not infrequently greater than those reported in patients with severely debilitating conditions such as spinal cord injury or cancers unresponsive to therapy.^[9] Improvement in HRQOL scores has been reported (e.g., increased exercise capacity and physical functioning) utilizing the currently available PAH-specific drugs.^[11–13]

Pathobiology

The postulated pathobiology of PAH involves interactions between the prostacyclin (PGI_2), endothelin (ET-1), and nitric oxide (NO) pathways, in addition to a host of other pathways (Fig. 1).^[2,14–16] Specific mechanisms responsible for the development and progression of PAH include the following: reduced PGI_2 synthase; increased ET-1 expression; decreased NO synthase; elevated plasma levels and low platelet 5-hydroxytryptamine levels; downregulation of potassium channels of pulmonary vascular smooth muscle cells; activity of autoantibodies and proinflammatory cytokines; and prothrombotic states arising from endothelial, coagulation, and fibrinolytic cascade/platelet dysfunction.^[16] These changes give rise to a complex process of pathobiologic changes in the pulmonary vascular bed, including endothelial dysfunction, vasoconstriction, vascular remodeling, and in situ thrombosis.^[2]

Pharmacologic targets of currently approved treatments for PAH

Current PAH treatment approaches include PGI_2 and its analogs, ET-1 receptor antagonists (ERAs), and phosphodiesterase type-5 (PDE-5) inhibitors.^[17] Combination trials have demonstrated additive and/or synergistic benefit by targeting more than one pathway.^[17] Prostanoid monotherapy (epoprostenol, treprostinil, and iloprost) improves symptoms, exercise capacity, and hemodynamics.^[17] Increased survival was also demonstrated in IPAH/heritable PAH (HPAH) with IV epoprostenol. However, common side effects with prostanoids include headache, flushing, nausea, jaw pain, diarrhea, skin rash,

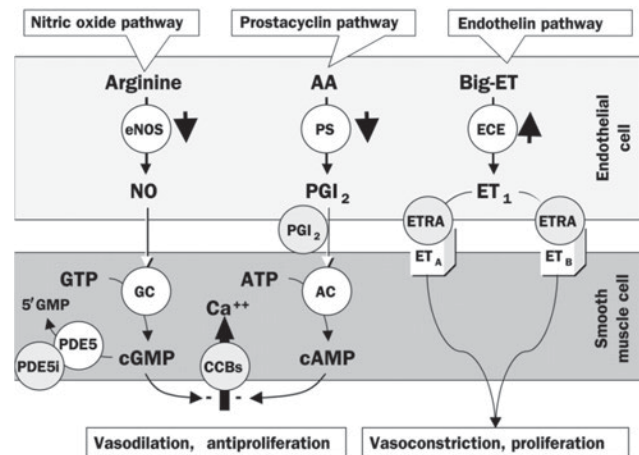


Figure 1: Pathways involved in the development and maintenance of pulmonary arterial hypertension. AA: arachidonic acid; ET: endothelin; eNOS: endothelial NO synthase; PS: prostacyclin synthase; ECE: endothelin-converting enzyme; PGI_2 : prostaglandin I_2 (prostacyclin); ETAR: endothelin receptor agonist; GTP: guanylate triphosphate; GC: guanylate cyclase; ATP: adenosine triphosphate; AC: adenylyl cyclase; CCBs: calcium channel blocker; cGMP: cyclic guanylate monophosphate; cAMP: cyclic adenosine monophosphate; PDE5: phosphodiesterase-5; PDE5i: PDE5 inhibitor. Reprinted from The Lancet, Vol. 358, Jocelyn Dupuis, Endothelin-receptor antagonists in pulmonary hypertension, pages no. 1113–1114, Copyright (2001), with permission from Elsevier^[15] and with permission from Mayo Clinic Proceedings, Volume 84, Michael D. McGoon and Garvan C. Kane, pulmonary hypertension: diagnosis and management, pp 191–207, Copyright Mayo Foundation for Medical Education and Research (2009).^[16]

and musculoskeletal pain. Treatment with PGI_2 and its analogs often requires continuous intravenous parenteral infusion, which can cause blood stream infections and/or thromboembolic events that can be life threatening.^[2]

Endothelin-1 exerts vasoconstrictor and mitogenic effects, whereas ERAs (i.e., bosentan and ambrisentan) improve exercise capacity, functional class, and hemodynamics.^[2,8] Adverse effects include acute hepatotoxicity, anemia, and fluid retention. Additionally, ERAs may cause testicular atrophy and male infertility. Use of bosentan requires monthly liver function tests and two modes of birth control, as it has been shown to cause severe fetal toxicity in animal studies.^[2,18]

In three randomized trials, the PDE-5 inhibitors sildenafil and tadalafil improved exercise capacity and hemodynamics (either as monotherapy or as add-on therapy).^[8,11,17] Both agents cause pulmonary vasodilation.^[8] Side effects include headache, flushing, and dyspepsia and are generally related to systemic vasodilation. Epistaxis has also been reported with sildenafil use in PAH.^[8,11] Prostacyclin analogs, ERAs, and PDE-5 inhibitors are the mainstays of current PAH treatment; however, all have systemic effects in addition to their pulmonary effects that can cause untoward side effects.^[19] An optimal agent for PAH therapy remains to be identified.^[17]

Inhaled nitric oxide

Inhaled nitric oxide (iNO) is a selective pulmonary vasodilator that can acutely decrease pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR) in neonates with hypoxic respiratory failure associated with pulmonary hypertension.^[20] Nitric oxide regulates vascular smooth muscle tone and increases blood flow to regions of the lungs with normal ventilation/perfusion ratios by dilating pulmonary vessels in better-ventilated areas.^[21] After inhalation, NO is absorbed systemically, with the majority of NO traversing the pulmonary capillary bed and combining with 60–100% oxygen-saturated hemoglobin.^[20] The effect of iNO is localized to the lung, as once absorbed iNO is rapidly oxidized by hemoglobin to form nitrite, which interacts with oxyhemoglobin, leading to the formation of nitrate and methemoglobin (metHb).^[20,22] This metabolic production of metHb is a potential toxic effect of iNO treatment. While doses <100 ppm most often result in insignificant metHb levels in adults and children, methemoglobinemia has been reported with 80 ppm when exposure was >18 hours.^[23]

Inhaled NO is currently indicated for the treatment of term/near-term neonates (>34 weeks gestation) with hypoxic respiratory failure associated with pulmonary hypertension (PH). The recommended dose is 20 ppm delivered via constant concentration during inspiration for up to 14 days or until hypoxia has resolved.^[20]

Inhaled NO has also been used as an agent for acute vasodilator testing (AVT) as part of the evaluation of PAH patients; doses of 20–80 ppm for 5–10 minutes are typically used.^[2,24] Detecting an acute response with AVT is useful in selecting patients who should be considered

for initial treatment with high-dose oral chronic calcium channel blockade; AVT response may also be helpful in predicting long-term prognosis with medical therapy and following surgical interventions, such as heart or heart–lung transplantation.^[24] Administered as continuous inhalation via face mask, iNO can selectively decrease PAP and PVR without reducing cardiac index or systemic vascular resistance.^[24] Inhaled NO has also been used in other contexts, such as perioperatively for cardiac surgery,^[25–33] right heart failure after insertion of the left ventricular assist device,^[34–37] cardiogenic shock due to right ventricle myocardial infarction,^[38] and pulmonary ischemia-reperfusion injury.^[39–44]

Because the pulmonary vasodilator effects of NO are transient, it is administered continuously during inspiration, with careful monitoring of NO and NO₂ concentrations.^[20] Nitric oxide gas can be safely administered in both intubated and nonintubated patients.^[45] The pulmonary selectivity of iNO may render it useful as an adjunct to other therapies that are dose limited by their systemic effects.

Inhaled NO has also been administered long term via pulsed nasal delivery (ml/breath/h) in clinical trials; this method has been studied for continuous long-term outpatient as well as short-term inpatient treatment (Fig. 2).^[46–49] This ambulatory administration method delivers a set, pulsed volume of NO at the beginning of each breath via a nasal cannula connected through a NO demand valve to a cylinder of up to 200 ppm NO in N₂.^[46–48] Both the continuous face mask and pulsed delivery via nasal cannula have comparable hemodynamic effects.^[50] A potential theoretical advantage of iNO, in contrast to IV vasodilators, is its

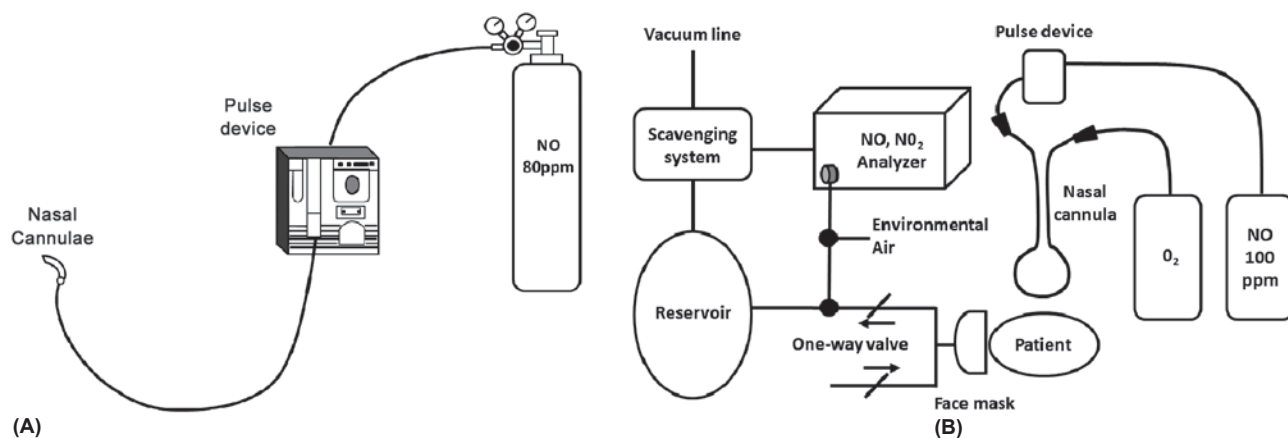


Figure 2: Examples of pulsed inhaled nitric oxide delivery systems used in clinical studies: (A) Ambulatory system. Reproduced with permission from the American College of Chest Physicians, Chest, Volume 109, Richard N. Channick, John W. Newhart, F. Wayne Johnson, Penny J. Williams, William R. Auger, Peter F. Fedullo, and Kenneth M. Moser, pulsed delivery of inhaled nitric oxide to patients with primary pulmonary hypertension: an ambulatory delivery system and initial clinical tests, pp 1545–1549, Copyright (1996), American College of Chest Physicians.^[48] (B) Hospital system. Reprinted with permission from Internal Medicine, Volume 41, Osamu Kitamukai, Masahito Sakuma, Tohru Takahashi, Jun Nawata, Jun Ikeda, and Kunio Shirato, hemodynamic effects of inhaled nitric oxide using pulse delivery and continuous delivery systems in pulmonary hypertension, pp 429–434, Copyright The Japanese Society of Internal Medicine (2002).^[49] iNO: inhaled nitric oxide NO₂: nitrogen dioxide

pulmonary selectivity (due to rapid hemoglobin-mediated inactivation).^[22] Although prostanoids administered via inhalation appear to have less ventilation-perfusion mismatching than when administered intravenously/subcutaneously or orally, some degree of ventilation-perfusion mismatching persists; in addition, systemic spill-over can result in untoward systemic effects.^[51-53]

CLINICAL APPLICATION OF INHALED NITRIC OXIDE AS LONG-TERM TREATMENT FOR PAH

Long-term (>1 month) pulsed iNO dosing appears to favorably affect pulmonary hemodynamics findings^[46-48,54,55]

which, with other types of therapy, appear to correlate with benefit (Table 1).

In a study of eight patients with IPAH, Channick et al. reported decreased mean PAP (mPAP), mean right atrial pressure (mRAP), and PVR ($P \leq 0.01$) with short-term iNO treatment using an ambulatory NO delivery system via nasal cannula (Table 1).^[48] No adverse symptoms and no changes in methHb levels were reported. One patient was discharged home on chronic pulsed iNO and reported no adverse effects after 9 months of treatment.

Ivy et al. also reported that in 26 children and young adults with PAH (short-term therapy, $n=24$; long-term therapy, $n=2$) constant concentration and pulsed delivery of NO (via nasal cannula) were equally effective in decreasing

Table 1: Inhaled long-term nitric oxide use for treatment of pulmonary arterial hypertension

Study	Study design	N	Age, diagnosis	Route of administration: Dose	Duration	Hemodynamic findings
Channick et al., 1996 ^[48]	Open label	8	NR, IPAH	<i>Pulsed iNO via cannula:</i> 80 ppm 0.1 sec pulse at 10 L/min	15 min ($n=8$); 24 h ($n=1$); 9 mo ($n=1$)	Decreased mean PAP (51–43 mm Hg), RAP (9–6.6 mm Hg), and PVR (790–620 dyne·s·cm ⁻⁵) ($P \leq 0.01$) Marked reductions in mPAP (>20%) and PVR (>30%) ($n=3$)
Ivy et al., 2003 ^[46]	Open label, controlled	26	1–24 y, PAH	<i>Pulsed iNO via cannula:</i> 100 ppm, alveolar concentration = 20 ppm <i>Adult:</i> 15–60 mL NO/ breath, flow rate = 10 L/min <i>Pediatric:</i> 3–10 mL NO/ breath, flow rate = 2 L/min	15 min ($n=24$), 7 mo ($n=1$), 2 y ($n=1$)	<i>Pulsed:</i> Decreased mean PAP (54–41 mm Hg), PVR (13.6 to 9.4 U·m ²), and RPSVR (0.62–0.41) ($P < 0.05$) <i>Continuous:</i> Decreased mean PAP (53 to 39 mm Hg), PVR (12.7–8.8 U·m ²), and PVR/SVR (0.58–0.38) ($P < 0.05$)
Pérez-Peñate et al., 2008 ^[47]	Open label, uncontrolled	11	31–78 y, severe PAH	<i>Continuous iNO via face mask:</i> 20 ppm	1 y ($n=9$)	Decreased mean PAP (64–58 mm Hg), PVR (1195–1016 dyne·s·cm ⁻⁵), and increased CI (2.1–2.2 liters/min/m ²) ($P \leq 0.04$) Also improved dyspnea, BNP level, and 6-min walk distance ($P \leq 0.02$)
Snell et al., 1995 ^[55]	Case report, open label	1	40-year-old female, end-stage PAH	<i>Pulsed iNO via face mask, then transtracheal Scoop™ catheter:</i> Mean: 50.4±23 ppm	68 d	Increased mean systemic BP (73–87 mm Hg), stabilized central venous pressure (21 mm Hg) and O ₂ saturation (92%) at 660 minutes
Pérez-Peñate et al., 2001 ^[54]	Case report, open label	1	32-year-old male, severe PAH	<i>Pulsed iNO via nasal cannula:</i> 80 ppm Flow rate = 0.9 L/min	1 y	Decreased mean PAP (78–72 mm Hg), PVR (1145–890 dyne·s·cm ⁻⁵) and increased CO (4.4–5.3 L/min) Also improved dyspnea, renal function, and edema after 20 d Improvement to NYHA Class II with no edema at 1 y

BNP: brain natriuretic peptide; **CI:** cardiac index; **CO:** cardiac output; **iNO:** inhaled nitric oxide; **NR:** not reported; **PAP:** pulmonary arterial pressure; **PVR:** pulmonary vascular resistance; **PVR/SVR:** ratio of pulmonary to systemic vascular resistance; **RAP:** right atrial pressure.

PAP and PVR ($P < 0.05$ vs. baseline; Table 1; Fig. 3).^[46] Adult and pediatric devices were studied, and the adult device delivered 15–60 ml NO per breath at a flow rate of 10 l/min while the pediatric device delivered 3–10 ml per breath at a flow rate of 2 l/minute. Two patients were discharged home on iNO using a pulsed device; 1 for 7 months and 1 for 2 years with no reported adverse events including no reports of syncope or near syncope.

Long-term treatment with pulsed iNO was evaluated in 11 patients (7 with PAH and 4 with chronic thromboembolic PH) in an uncontrolled, open-label study. The study design included the addition of PDE-5 inhibitor (dipyridamole or sildenafil) for clinical worsening; this was suggested as a means to “stabilize and potentiate the effects of iNO” and to “potentially serve as rescue therapy in severe PH” (Table 1).^[47] After 1 month of an ambulatory iNO system via nasal cannula, patients had an improvement in World Health Organization functional class concomitant with improvements in 6-minute walking distance ($P = 0.003$), and brain natriuretic peptide (BNP) level ($P = 0.02$; Fig. 4).^[47] One patient died from refractory right heart failure at month 8; 7 of the 11 patients had a PDE-5 inhibitor added at 6–12 months due to symptomatic deterioration. At the 1-year follow-up, 9 of the 11 patients reported durability of effect as observed after 1 month of therapy with associated significant improvements in mPAP, PVR, and CI. In addition, the significant improvements in 6-minute walking distance ($P = 0.003$) and BNP levels ($P = 0.02$) were maintained at the 1-year follow-up. There were no reports of NO air contamination, changes in methHb levels, adverse reactions, NO toxicity, or rebound PH from sudden withdrawal.^[47]

Two case reports have also examined long-term iNO administration in PAH patients, including its use as a “bridge to heart-lung or lung transplantation” (Table 1). A 40-year-old woman presented with end-stage IPAH and experienced severe dyspnea, right ventricular angina, oliguria, and syncope despite treatment with dopamine infusion and with prostacyclin. The patient then initiated treatment with pulsed iNO, initially via face mask and then transtracheal catheter, until she underwent heart-lung transplantation after 68 days of therapy.^[55] The patient's condition appeared to stabilize on iNO treatment, although she had a hypotensive bradycardic event after 53 days, requiring reinitiation of intravenous prostacyclin. While iNO was administered, she was able to move about her room independently and participate in a physiotherapy exercise program. The explanted lungs revealed no evidence of NO toxicity.^[55]

Another case reported the effects of 12 months of iNO administration in a 32-year-old man with IPAH (Table 1).^[54] The patient presented with exertional dyspnea and

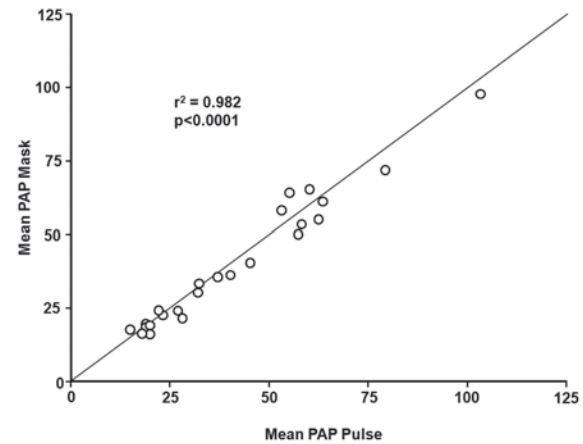


Figure 3: Correlation between mean pulmonary arterial pressure during mask delivery and pulsed nasal nitric oxide delivery. PAP: pulmonary artery pressure. Reprinted from *The American Journal of Cardiology*, Vol 92, D. Dunbar Ivy, Donna Parker, Aimee Doran, Donna Parker, John P. Kinsella, and Steven H. Abman, acute hemodynamic effects and home therapy using a novel pulsed nasal nitric oxide delivery system in children and young adults with pulmonary hypertension, pages no. 886–890, Copyright (2003), with permission from Excerpta Medica, Inc.^[46]

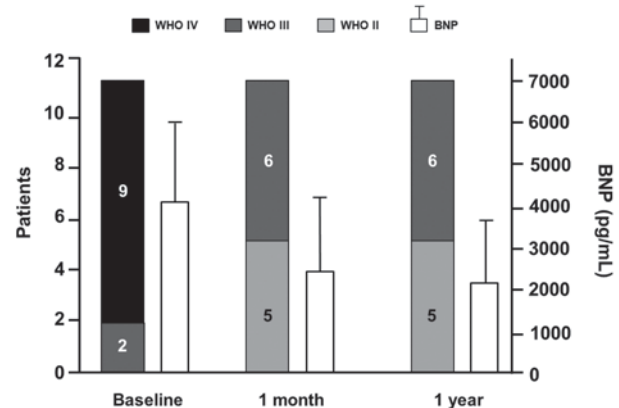


Figure 4: World Health Organization functional class and brain natriuretic peptide levels (mean±SD) at baseline compared with 1 month and 1 year after onset of iNO treatment. *In Patients 1 and 2, the measure was taken at 6 months. BNP: brain natriuretic peptide. Reprinted from *The Journal of Heart and Lung Transplantation*, Vol 27, Gregorio Miguel Pérez-Peñate, Gabriel Juliá-Serdà, Nazario Ojeda-Betancort, Antonio García-Quintana, Juan Pulido-Duque, Aurelio Rodríguez-Pérez, Pedro Cabrera-Navarro, Miguel Angel Gómez-Sánchez, Long-term inhaled nitric oxide plus phosphodiesterase 5 inhibitors for severe pulmonary hypertension, Pages No. 1326–1332, Copyright (2008), with permission from the International Society for Heart and Lung Transplantation.^[47]

anasarca, and was treated with long-term iNO monotherapy via an ambulatory system with nasal cannula. After 20 days, there was an improvement in dyspnea and gas exchange, and a resolution of the anasarca. After 12 months of continuous iNO, the patient remained clinically stable, with maintained hemodynamic improvement and no signs of toxicity or tachyphylaxis.^[54]

Ivy et al. reported that short-term pulsed nasal delivery utilizing constant concentration was as effective in lowering PAP and PVR as mask delivery in the acute setting in eight children with PAH (Fig. 5).^[50] Based on the results of this study, the authors concluded that the practicality of long-term iNO therapy via pulsed flow nasal delivery is potentially dependent on four factors: (1) maintenance of sufficient iNO delivery; (2) improvement of hemodynamic derangements by nasal cannula at low flow rates; (3) effective delivery of nasal NO with minimal release of gas into the environment; and (4) minimized consumption of NO gas.^[50] Aside from the reports involving long-term use summarized in Table 1, the practicality of pulsed delivery of iNO for improvement in oxygenation with less NO consumption and less environmental contamination has been demonstrated in several other studies.^[56-58]

ROLES FOR LONG-TERM INHALED NITRIC OXIDE IN THE TREATMENT OF PULMONARY ARTERIAL HYPERTENSION

Potential uses of pulsed, long-term iNO treatment in PAH patients include the following: use as a bridge to transplantation; a means of deferring transplantation; and as an add-on therapy to currently approved PAH drugs^[2,45] with potential additive or synergistic effects.^[59,60] It is important to note that NO synthase 3 (NOS3) has been reported to be decreased in PAH patients; in uncontrolled observational studies, PAH has been associated with impaired NO release, at least in part, due to reduced expression of NOS3 in the vascular endothelium of pulmonary arterioles.^[61] As a result, long-term administration of iNO may serve both as a selective pulmonary vasodilator and as NO replacement therapy, making it a logical choice for clinical evaluation as add-on therapy.

Safety considerations

A potential safety concern with iNO treatment is rebound PH upon its sudden discontinuation after longer-term (days) use^[20,62]; this phenomenon is well known and has been well documented in neonates and in postoperative cardiac surgery patients. Such patients include cardiac transplant recipients, children undergoing surgery for congenital heart disease, and adults with mitral and/or aortic stenosis. Gradual weaning of iNO has been shown to minimize the potential for rebound PH in the acute ICU setting.^[45] Davidson et al. presented a method to safely withdraw iNO in infants treated for hypoxic respiratory failure, recommending the gradual weaning of iNO down to 1 ppm prior to treatment discontinuation.^[63] Further research has implicated the rapid degradation of smooth

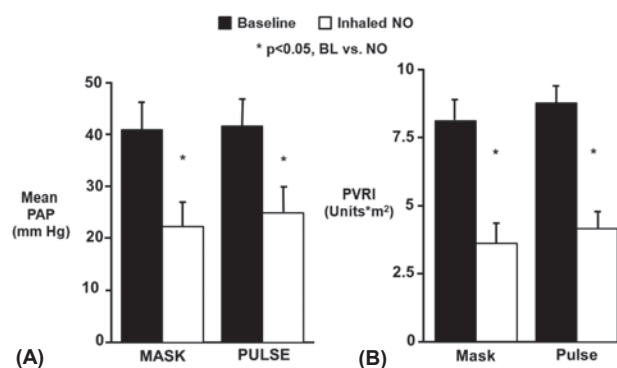


Figure 5: Delivery of inhaled NO by continuous mask or pulsed nasal cannula was equally effective in lowering mean pulmonary artery pressure (A) and pulmonary vascular resistance index (B). PAP: mean pulmonary artery pressure; PVRI: pulmonary vascular resistance index; iNO: inhaled nitric oxide; BL: baseline. Reprinted from *The Journal of Pediatrics*, Vol 133, D. Dunbar Ivy, Jeffrey L. Griebel, John P. Kinsella, and Steven H. Abman, acute hemodynamic effects of pulsed delivery of low flow nasal nitric oxide in children with pulmonary hypertension, Pages No. 453–456, Copyright (1998), with permission from Mosby, Inc.^[50]

muscle intracellular cyclic guanosine monophosphate (cGMP) by local phosphodiesterases (PDEs) as a primary mechanism for this rebound effect. As a result, initial approaches focused on the use of dipyridamole, a PDE-5 inhibitor, as a means for reducing rebound PH after iNO withdrawal. Ivy et al. first demonstrated this concept in a prospective study of 23 children treated with iNO after surgery for congenital heart disease.^[64] Later studies examined the role of sildenafil, another PDE-5 inhibitor, in the context of rebound PH, showing that its introduction prior to withdrawal of iNO resulted in facilitation of iNO weaning, as well as prevention/amelioration of rebound PH effects in infants and children with PH after congenital heart disease surgery, persistent PH of the newborn, and other abnormalities.^[65-68] As with any approach, it is important to consider patient characteristics and treatment familiarity, availability, and contraindications, as well as optimal ventilation and supplemental vasodilators, when initiating treatment for rebound PH.^[66]

A review of the published literature on long-term iNO dosing in PAH patients has not revealed any reports of rebound PH crises or associated symptoms (e.g., syncope, systemic arterial oxygen desaturation, systemic hypotension, bradycardia, or cardiac arrest).^[46-48,54,55] It may be that more acute initial rise in PAP is associated with a greater likelihood and severity of a rebound effect occurring with acute iNO withdrawal. This may explain why the rebound phenomenon has been observed in the acute care setting (e.g., neonates with persistent pulmonary hypertension of the newborn and high risk postoperative cardiothoracic surgical patients) and not observed in the more chronic setting of PAH or chronic obstructive pulmonary disease.^[69]

Cytotoxicity is another possible concern with iNO and its oxidized derivatives (principally NO₂). Nitric oxide may be directly toxic to alveolar and vascular tissue; therefore, it has been proposed that NO be stored in combination with nitrogen and blended with oxygen at the time of administration to prevent oxidation to toxic products, in addition to maintaining NO₂ levels <5 ppm.^[23,70]

CONCLUSIONS AND FUTURE DIRECTIONS

In summary, uncontrolled observational studies of long-term use (>1 month) of continuous pulsed iNO (as monotherapy or as part of combination therapy) in a total of 14 patients with PAH across five studies^[46-48,54,55] have reported no significant adverse events, no elevated methHb levels, and no detectable exhaled or ambient NO or NO₂. In one study, a patient experienced three episodes of severe epistaxis over two years while on a combination of pulsed iNO and epoprostenol.^[46] In a case report of a patient awaiting heart-lung transplantation, the patient experienced hypotensive bradycardia upon an attempt to wean from iNO therapy. In addition, a recurrence in hypotensive bradycardia resulted in the increase of iNO dose (40–106 ppm), followed by a decrease to 70 ppm (along with administration of bicarbonate and reintroduction of prostacyclin) after increasing metabolic acidosis.^[55]

There is evidence that pulsed delivery may allow utilization of lower NO concentrations compared with continuous face mask administration, potentially minimizing the risk of associated adverse events as well as resulting in a more practical delivery system.^[49]

The consensus on treatment for PAH encompasses numerous goals, the most important being to improve overall quality of life by decreasing symptoms while minimizing treatment-related side effects.^[2] Additional goals include enhancing functional capacity, i.e., exercise capacity, improving hemodynamic derangements (lowering PVR and PAP, and normalizing RAP and CO), and preventing, if not reversing, disease progression. Finally, improving survival, although certainly desirable, is rarely an end point in trials examining PAH treatment.^[2] The availability of novel treatments and the improvement in survival rates have allowed the goals of PAH therapy to expand from improving survival and preventing disease progression to also improving HRQOL.^[71] Potential advances in long-term PAH treatment, such as ambulatory iNO administration, may allow for greater improvements in HRQOL. Pérez-Peñate et al. observed that ambulatory pulsed iNO treatment did not diminish quality of life beyond the consequences of the disease itself.^[47] Eight of

eleven patients who led a nonsedentary life were able to leave their home daily, with four returning to work while on long-term iNO therapy.

An ideal drug-device for long-term PAH treatment should emphasize portability and safety features for outpatient use. Advances in iNO gas delivery technology and strategies to optimize dosing should allow for randomized controlled trials of iNO and, hopefully, may lead to broad-scale application of iNO in the treatment of chronic diseases such as PAH.^[45]

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EXHIBIT 11



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Practical considerations in the management of inhaled prostacyclin therapy for pulmonary hypertension associated with interstitial lung disease (WHO group 3)

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ABSTRACT

Pulmonary hypertension (PH), as a consequence of lung disease or hypoxia, has been classified as Group 3 PH by the World Symposium on Pulmonary Hypertension. The most common lung diseases associated with Group 3 PH are chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD). PH in ILD (PH-ILD) is associated with reduced exercise capacity, greater supplemental oxygen needs, decreased quality of life, and earlier death compared to ILD alone. Several agents have been evaluated in clinical trials for the treatment of Group 3 PH, but only one treatment has been recently approved by the FDA as conclusively demonstrating efficacy for the treatment of pulmonary hypertension in this group. In the INCREASE study, treprostinil inhalation solution (Tyvaso) demonstrated significant clinical benefit for patients with PH-ILD. The inhaled route of administration may be associated with cough, throat irritation, pharyngolaryngeal pain and risk of bronchospasm and are important considerations upon initiation of therapy. Here we provide a practical review of inhaled prostacyclin therapy and suggestions for healthcare professionals to optimize the management and outcomes for the treatment of WHO Group 3, PH-ILD patients. Recommendations include up-to-date practical considerations pertaining to the entire care team and encompass patient education and communication, monitoring, titration methods and mitigation of side effects.

1. Introduction

Pulmonary hypertension (PH) is defined as an elevation in mean pulmonary arterial pressure (mPAP) of >20 mmHg, accompanied by a pulmonary vascular resistance (PVR) of ≥ 3 Wood Units [1]. The World Symposium on Pulmonary Hypertension has categorized PH into five groups, based on characteristic pathophysiology, etiologies, clinical presentation, hemodynamic characteristics, and therapeutic management. Group 1 describes pulmonary arterial hypertension (PAH) and includes diverse diseases that all result in similar pathological changes within the pulmonary vasculature. Group 1 PAH is noted as being particularly aggressive in nature, with poor survival [2]. PH, as a consequence of lung disease or hypoxia, has been classified as Group 3. The most common lung diseases associated with Group 3 PH are chronic obstructive pulmonary disease (COPD) and interstitial lung disease

(ILD), the latter characterized by inflammation, marked scarring or fibrosis in the lungs, resulting in arterial thickening and PH. PH in ILD (PH-ILD) is associated with reduced exercise capacity, greater supplemental oxygen needs, decreased quality of life, and earlier death compared to ILD alone [3,4].

Until very recently, there have been no approved therapies for the treatment of Group 3 PH patients. Although several agents had been previously evaluated in clinical trials for the treatment of Group 3 PH patients, none had conclusively demonstrated efficacy for the treatment of pulmonary hypertension in this group [5–12].

In April 2021, the United States Food and Drug Administration (FDA) approved treprostinil inhalation solution (Tyvaso, United Therapeutics Inc.) to improve exercise ability for patients who have PH associated with ILD (PH-ILD) based on results of the INCREASE study, which demonstrated significant clinical benefit to this patient group.

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Treprostinil is a chemically stable tricyclic analogue of prostacyclin, which promotes direct vasodilation of pulmonary and systemic arterial vascular beds and inhibits platelet aggregation [13]. Inhaled treprostinil was originally approved in 2009 for the treatment of WHO Group 1 PAH. Based on nearly a decade of experience in PAH patients, the pivotal INCREASE study was designed to evaluate inhaled treprostinil in 326 adult patients with Group 3 PH-ILD [14]. Inhaled treprostinil was well tolerated and patients experienced significant improvements in exercise capacity as early as 8 weeks, with a placebo-corrected improvement from baseline in peak 6MWD of 31 m at 16 weeks. Additionally, patients treated with inhaled treprostinil demonstrated improvements in other clinically meaningful outcomes, including significant reductions in NT-proBNP, clinical worsening events, and lung disease exacerbations compared to placebo. Exploratory analyses also demonstrated inhaled treprostinil resulted in improvement in percent predicted FVC at week 8 (1.79%; $P = 0.01$) and week 16 (1.80%; $P = 0.03$) [14].

As observed in the INCREASE study, there are potential side effects associated with the inhaled route of administration, including cough, throat irritation, and pharyngolaryngeal pain [14]. Often, healthcare professionals are tasked with supporting patients through the side effects and practical challenges related to inhaled treprostinil therapy and its administration. In 2011, Poms and Kingman published an insightful review on the use of inhaled treprostinil in Group 1 PAH patients including recommendations for practical management of side effects in these patients [15]. A few years later, Farber and colleagues shared their experience and practical suggestions for supporting patients and healthcare professionals in addressing the complexities of PAH treatment with prostacyclin therapies to encourage compliance and optimize outcomes [16]. The previous work related to PAH treatment provided a valuable foundation for the current understanding of inhaled treprostinil treatment in PH-ILD. In light of recent advancements in inhaled treprostinil therapy, an update to the practical guidance for implementation of inhaled therapy into clinical practice is timely and essential to optimize effectiveness.

Four healthcare professionals were approached to aid in the development of clinical pearls and practical guidance to optimize therapy with inhaled treprostinil. These clinicians represented varying healthcare disciplines from different geographies and were selected based on their experience using inhaled treprostinil in patients with PAH and PH-ILD and patient enrollment into the INCREASE trial. After selecting these clinicians and confirming their interest, two virtual interview sessions were conducted to reflect on published literature and share best practices and real-life experience with inhaled treprostinil. A question/answer session was included as part of each virtual meeting. Clinicians discussed their first-hand experience with the methods applied and management experience of PAH and PH-ILD patients in pulmonary hypertension care centers and major PH programs in their respective areas. Based on the discussions during the interview sessions, a summary of recommendations was drafted and circulated to the clinicians for review.

Based on the published literature and the authors' expertise and experience with inhaled treprostinil delivery, we provide important considerations for the management of inhaled prostacyclin therapy in PH-ILD in WHO Group 3 patients. Recommendations include up-to-date practical considerations affecting the entire care team and encompass patient education and communication, monitoring, titration methods and mitigation of side effects.

1.1. Setting up for success - onboarding

Some of the most important factors in successful inhaled treprostinil administration occur prior to the patient's first dose. Studies have demonstrated that patient instruction plays a central role in disease management and that effective education can have a significant impact on disease control [17]. Patient education about the device, dosing, safety, and efficacy of treatment and setting expectations related to

side-effects and outcomes are critical to success. Equally important is ensuring patients are familiar with other potential members of their care team, including their specialty pharmacy.

PH-ILD patients presented with the potential benefits of inhaled treprostinil as a new treatment option may be apprehensive about starting any treatment that is new to them, or that has been recently approved. It can be helpful to advise patients that although inhaled treprostinil has been recently approved for PH-ILD, the medication has successfully been administered via nebulization to treat other patients for over a decade. Reinforcing that the treatment is not new, but that studies have now shown that it can be beneficial for this patient population can help to instill confidence in the PH-ILD patient. This, combined with the support of the care team in being able to offer a new treatment option, may alleviate patient apprehension.

When starting therapy with inhaled treprostinil, it is important to emphasize the potential benefits and side effects of treatment, while underscoring the commitment required on behalf of the patient. Commitment to treatment and perseverance during titration will enable patients to reach a target dose that can improve their symptoms and functional status. Learning the appropriate breathing technique, the frequency of treatment, and the daily preparation of medication and assembly and cleaning of the device may seem daunting at first, but as the patient's comfort level with the device improves, so does their confidence to continue. Patients can expect the best opportunity for clinical improvement with this treatment if they are able to commit to the process and dosing regimen.

1.2. Practical considerations of administration

Inhaled treprostinil solution is dosed using the Tyvaso Inhalation System, which consists of an ultrasonic, pulsed delivery device and accessories (Fig. 1). An important foundation for success is teaching the correct use of the device and mastering the technique of taking proper breaths. The patient may not understand that the device will be different than an inhaler or nebulizer that they have used in the past and be surprised by the differences in breathing technique. Patients are advised to take in a normal, full breath lasting approximately 3 s, and then exhale with their mouth removed from the mouthpiece. It is important to remind patients that treatment only takes a few minutes, not up to 20 min that is typical of other nebulizer therapies [18] and that once the device is set-up in the morning it can be used for every treatment session that day (see Fig. 2).

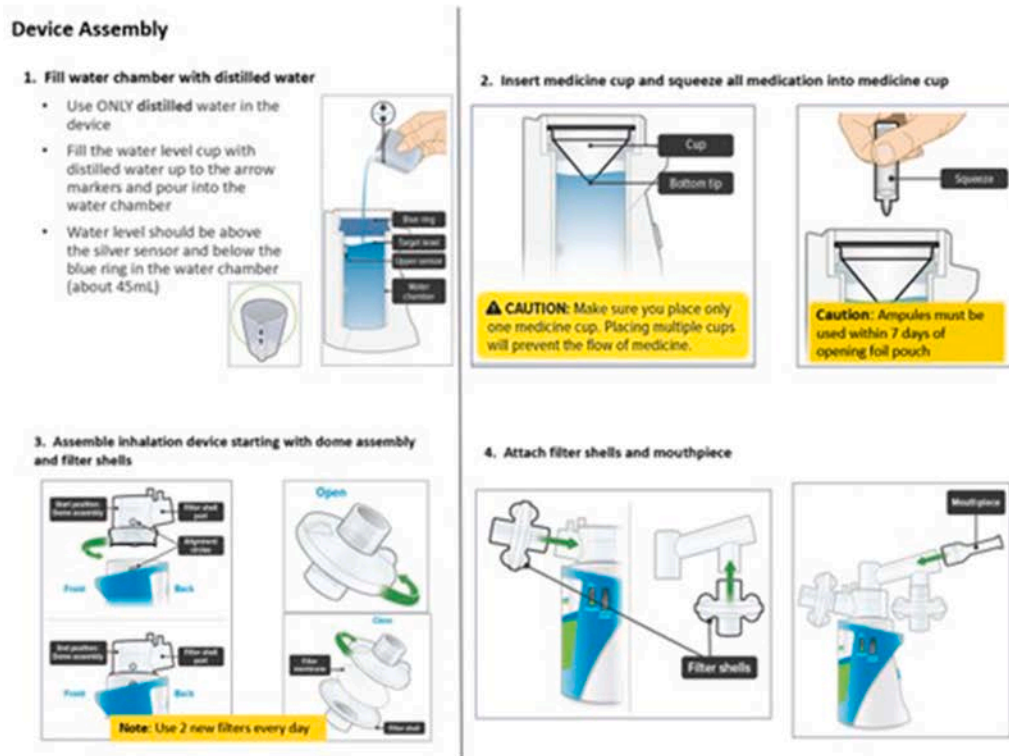
Treprostinil dosing is measured in breaths and one breath is equivalent to approximately 6 mcg of treprostinil. Inhaled treprostinil solution should be administered four times daily, with treatment sessions scheduled approximately 4 h apart, during waking hours. The standard titration schedule begins with an initial dose of 3 breaths (18 mcg) per treatment session and may be increased gradually, by an additional 3 breaths per session at approximately 1–2 week intervals based on tolerability of side effects [19]. If side effects occur, the titration schedule can be adjusted as needed to 1–3 breaths per session every 3–14 days. In the INCREASE study, patients up-titrated on average by 1 breath per session, as often as every 3 days, until they reached a target dose of 9 breaths with most patients achieving it by week 8 [14]. Although the target dose was 9 breaths, many patients achieved the maximum dose of 12 breaths by week 16. Target doses are consistent with the INCREASE study, typically 9 to 12 breaths per treatment session, four times daily. The device allows for titration increments of one breath. Target dosing and up-titration are individualized, however, based on the patient's ability to tolerate the associated side-effects and assessed clinical benefit.

1.3. Communication and the care team

Delivery of inhaled treprostinil to PH-ILD patients requires open lines of communication among the entire care team, including patients,



A



B

Fig. 1. Inhaled treprostinil device (A) and assembly and medication preparation (B).

caregivers, clinical coordinators and specialty pharmacy that dispenses medications and provides virtual and in person nursing support (Fig. 3, Table 1). There is considerable evidence that suggests that patient engagement improves outcomes. Specific to pulmonary disease, patients who feel well-informed and receive comprehensive guidance, find it easier to cope with their disease and have demonstrated better outcomes [20,21]. If patients develop side-effects, it is essential that they know who to contact to help guide them through dose adjustments or help manage adverse events. The presence of a family member or caregiver during clinical discussions and education sessions is an additional resource that may aid in retention of information about the disease and treatment plan [22].

It is important that patients feel supported during the entire treatment journey and have a network of resources to address their questions

or concerns. These may include online connections, in-person support groups, patient volunteers or other patients with treatment experience, often organized by patient advocacy groups or medical associations.

Maintaining good communication between all members of the care team is integral in providing consistent and optimized care to the patient. Often at the initiation of therapy all members of the care team are very involved with the patient and each other, however as the patient becomes more stable, interactions may become less frequent. The patient may have communication regarding therapy with one member of the care team, such as the specialty pharmacist, however this communication may not be relayed to the entire team, leaving some unaware of a patient's challenges or changes in therapy. Establishing a communication plan between all members of the care team, particularly between the specialty pharmacy and clinical team, is fundamental to delivering



Fig. 2. Clinical pearls for proper breathing technique for inhaled treprostinil solution. Take a normal, full breath for 3 s. Do not hold breath once medication is inhaled. Use start/stop button to pause as needed for coughing or treatment interruptions. Keep the Tyvaso device level during treatment to direct the flow of medication into the airway.

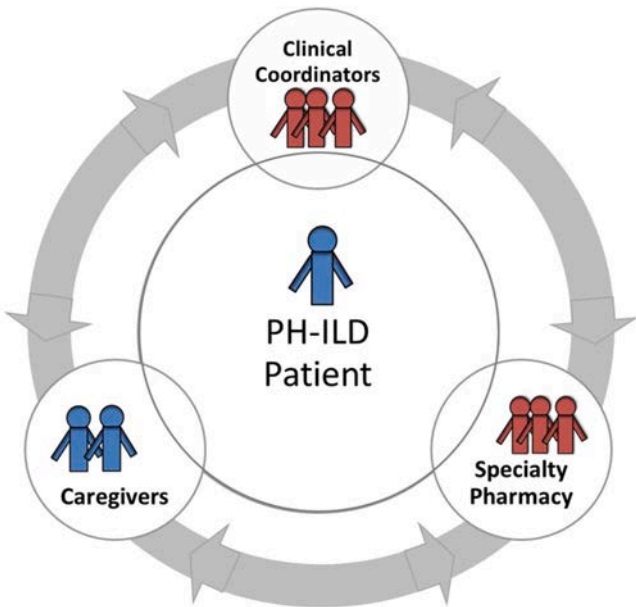


Fig. 3. Team members involved in the care of the PH-ILD patient.

the best possible consistent level of care. Utilization of specialty pharmacy resources such as appointed pharmacy liaisons, weekly patient reports and provider portals may help to ensure that all team members have access to all patient-related communication. The specialty pharmacy generated patient roster may include trackable updates related to medications, dose changes, preauthorization status, and patient-reported issues.

Based on the studies that established the effectiveness of inhaled treprostinil in patients with PAH and PH-ILD, the dosing target is 9–12 breaths per treatment session, 4 times daily [19]. The effectiveness of inhaled treprostinil is a function of up-titration and the ability to achieve the maximum tolerated, clinically appropriate dose for each individual

Table 1 Roles of the care team.	
Care Team Member	Care Team Role
Clinic Staff (physicians, advanced practitioners, nurses, medical assistants, clinic pharmacists, etc.)	<ul style="list-style-type: none">● Responsible for prescription, referral, and prior authorization submission for inhaled treprostinil● Educate on disease and medications● Provide tools to assist with management of medication side effects● Manage medication titration to reach optimal stable dose● Serve as point of contact between patient and specialty pharmacy
Specialty Pharmacy (specialty pharmacy nurses, pharmacists, and pharmacy technicians/liaisons)	<ul style="list-style-type: none">● Process initial referral and contact insurance company to determine and verify coverage● Provide initial drug/device training and ongoing support● Serve as liaison between clinical staff and patient● In collaboration with clinical team, assist with side effect management and medication titration● Arrange for follow-up and ongoing shipment of supplies
The Patient/Caregiver	<ul style="list-style-type: none">● Caregiver provides patient support● Participate in device training, set-up, and management● Communicate treatment issues to clinical staff and specialty pharmacy team● Notify clinical staff and specialty pharmacy of insurance changes or financial needs

Treatment Regimen and Titration.

patient. Results from the INCREASE study demonstrated that achieving higher doses was associated with improved clinical effect, specifically improvements in 6MWD and clinical worsening [14 suppl]. Additionally, in a post-hoc analysis of INCREASE study data, there has been an observed link between higher doses and decreased rates of clinical worsening and death [23]. For PAH patients, up-titration by 3 breaths per session is recommended, at approximately 1–2 week intervals and for those with PH-ILD, up-titration of 1 breath per week is recommended.

It is important that patients understand that treatment with inhaled treprostinil is individualized and progresses in a stepwise manner. The care team should establish treatment goals at the onset of therapy and emphasize flexibility in dosing. For example, if a patient is not able to tolerate the starting dose of 3 breaths, it can be reduced to 1 or 2 breaths and subsequently increased to 3 breaths, as tolerated [19]. Making titration adjustments on a regular weekly schedule may simplify the regimen and improve patient adherence. Achieving the target of 9–12 breaths per treatment session is quite common, and further increases may be considered on an individual basis. As patients gain experience and success with inhaled treprostinil, the treatment goals can be re-evaluated, and the plan adjusted accordingly.

1.4. Compliance

Follow-up visits provide the opportunity to assess the patient's progress and impression of therapy, as well as emphasize key teaching points. Reinforcing device positioning and breathing technique will help to ensure that the patient is performing the breathing maneuvers appropriately. If the patient's scheduled treatment occurs during their appointment time, the team member can observe their technique and provide helpful feedback, if necessary, and also assess the patient's compliance with therapy. Non-compliance may be related to side-effects, but it is also important to consider that patients may feel they

are too busy to adhere to the recommended schedule. Non-compliance may also occur because patients are perhaps feeling better or more comfortable, resulting in sub-optimal compliance with treatment. Many patients have success adhering to their recommended treatment schedules by setting reminders or alarms on their phones or smartwatches. Adherence may be assessed by checking Specialty Pharmacy records or by simply asking the patient if they are having any difficulties managing their prescribed number of treatments per day. Patients may be reluctant to acknowledge missed treatments, therefore the tone of the conversation needs to be positive and supportive with the goal of helping the patient optimize their outcomes on inhaled treprostinil therapy.

Compliance can also be assessed by comparing results of objective clinical measurements and non-invasive testing across previous visits. If a patient has worsened compared to a prior visit, this may signal a compliance issue. Presenting the worsening measurements to the patient creates an opportunity to discuss potential compliance challenges and how to address them.

1.5. Side-effects: expectation and mitigation

In the INCREASE study, 43.6% of patients treated with inhaled treprostinil solution experienced cough, 27.6% experienced headache, 12.3% reported throat irritation and 15.3% reported some nausea; similar to the side effects reported in Group 1 PAH trials, although treatment discontinuation due to side effects was shown to be relatively low and comparable to the placebo group [14,24]. It is important that patients understand that if these side effects occur, it does not mean they are having a “bad reaction” or are allergic to treatment. These side effects are related to the medication and the route of delivery and can often be managed with assistance from their care team.

In addition to being aware of the potential side-effects, discussing the severity and duration of side-effects can be helpful. Patients need to be aware that they may not feel well during the first few days following a dosing adjustment or up-titration but the side effects may lessen or completely resolve with time. Keeping close contact and directing the patient to communicate with their care team if they are not improving will provide an opportunity to adjust dosing or provide supportive intervention. It is important that patients feel comfortable and ready to up-titrate even if this means taking additional time to manage side-effects. The goal is to support the patient through the titration period as they reach their stable dose.

Cough is a primary complaint with inhaled treprostinil therapy and needs to be at the forefront of any side effect discussion. Many PH-ILD patients have a baseline cough, which may worsen with administration of inhaled treprostinil. It is important to emphasize cough associated with inhaled treprostinil tends to only occur around treatment time and does not persist throughout the day. Patients on inhaled treprostinil should be advised to be proactive and pre-treat whenever possible.

For patients experiencing a treatment-related cough, it is recommended that the first step be to review treatment administration technique. Often, simple adjustments to breathing technique or to the positioning and holding of the device can reduce the severity of or alleviate the cough. If cough persists, aids such as swallowing a small amount of yogurt, honey, peanut butter or drinking something cold or warm to soothe the patient's throat prior to treatment may be beneficial. Short acting bronchodilators, including albuterol, an inhaled beta agonist, can relax bronchial smooth muscle and open the airway, while throat pain relievers, such as Chloraseptic spray act as temporary analgesics.

If patients develop worsening dyspnea, they should be reevaluated for any clinical changes such as volume status, oxygenation and/or underlying airways disease as a potential cause. Additionally, during treatment sessions, patients may experience temporary shortness of breath, particularly as the number of breaths per session increases. If dyspnea occurs during treatment, patients can briefly pause their session, by pressing the stop/start button on the device, to catch their

breath and then resume inhalations to complete the treatment session.

Other common side effects associated with inhaled treprostinil therapy include gastrointestinal issues and headache. If a patient experiences nausea following treatment, the first step should be to re-evaluate the position of the device to ensure it is being held level and medication delivery is being directed toward the airway. Incorrect holding of the device/placement of the mouthpiece results in medication being deposited on the tongue and subsequently swallowed, which can cause nausea and potentially diarrhea. If nausea persists following a treatment session, it is recommended that patients swish their mouth with water and spit to remove any remaining medication from the mouth. Loperamide is used to help manage the symptoms of diarrhea. Acetaminophen is recommended for headache (Table 2).

Patients that are on multiple medications should receive special consideration and simultaneous onboarding of different medications should be avoided, when possible, to lessen side-effects. Concomitant medications, such as antifibrotics, may lead to an increase in gastrointestinal-related side effects, emphasizing the need to preemptively manage these side effects to the extent possible [25].

1.6. Treatment outcomes

It is important to present the benefits of inhaled treprostinil therapy and ensure that patients are well educated about what they can expect in relation to their PH symptoms. They may need to be reminded that they did not arrive at their current degree of symptoms overnight, and therefore it is not reasonable to expect a dramatic improvement in their symptoms in a short period of time. Naturally, patients will want to know when they can anticipate noticeable improvement. It is recommended to frame these discussions around their baseline symptoms. For example, advising patients that they may experience shortness of breath less often, recover more quickly or feel less exertion moving from room to room or from the bed to the commode. Setting patient-specific benchmarks may help them to recognize functional capacity improvements, such as walking to the mailbox with less shortness of breath. Family members or caregivers can also be helpful in identifying small improvements, and over time, building toward bigger improvements. The key is to set realistic expectations based on the patient's current abilities and exercise capacity and set long term goals appropriately.

1.7. Future directions

Most recently, the results of a study evaluating a treprostinil dry powder inhaled formulation using a small portable inhaler for patients with PAH was released. The device and formulation have the potential to provide improved convenience and thus better compliance with treatment. The BREEZE study included 51 patients with Group 1 PAH already on nebulized inhaled treprostinil (Tyvaso) who transitioned to the dry powder formulation and device [27] (Fig. 4). They demonstrated that the transition was safe and well tolerated with significant improvements in 6MWD (+11.5 m), device preference and satisfaction, and patient reported outcomes after only 3 weeks of treatment [27]. Similar to previous inhaled treprostinil studies in patients with PAH, 35% experienced cough, and 16% reported headache.

1.8. Conclusions/summary

Being well versed on inhaled treprostinil, both the medication and the device, the realistic benefits and expected side effects, is crucial to success of treatment. Including the patient in all the discussions and establishing the clear lines of communication with frequent touch points will provide the best opportunity for patients to meet their treatment goals. This is particularly important during the initial dosing and titration process. Encouraging the patient to continue with treatment at their own pace and assisting them through up-titration will give them the best opportunity for improvement.

Table 2

Possible adverse events associated with inhaled treprostinil solution and interventions for mitigation.

Adverse Event	Frequency of Occurrence in INCREASE study [14]	Suggested Interventions for Mitigation
Cough	43.6% (n = 71)	<ul style="list-style-type: none"> ● Re-evaluate breathing technique ● Slow breathing pace or pause between breaths ● Drink warm or very cold water prior to treatment ● Eat a spoonful of yogurt, peanut butter or honey prior to treatment ● Cough medicine (over the counter or by prescription), but cough drops should be avoided due to increased aspiration risk ● Short-acting bronchodilator ● Oral phenol-based analgesic sprays (Chloraseptic) ● Consider adjusting or optimizing airway medications
Headache	27.6% (n = 45)	<ul style="list-style-type: none"> ● Anti-inflammatory medication or acetaminophen ● May resolve over time without mitigation ● Slow titration schedule if severe headache persists ● Decrease dose and attempt re-titration once headache has subsided
Dyspnea	25.2% (n = 41) *31.3% in placebo group	<ul style="list-style-type: none"> ● Reevaluate for any clinical changes such as volume status, oxygenation and/or underlying airways disease ● For dyspnea during treatment, use the start/stop button to temporarily pause inhalations and resume when shortness of breath resolves
Dizziness	18.4% (n = 30)	<ul style="list-style-type: none"> ● Decrease and/or slow down inhaled treprostinil dose titration ● Re-evaluate breathing technique: normal breathing pattern, no deep breath or breath hold, utilize device pause button between breaths ● Monitor BP and fluid intake and adjust other blood pressure lowering medications as appropriate
Nausea	15.3% (n = 25)	<ul style="list-style-type: none"> ● Re-evaluate breathing technique to ensure level holding of the device ● Anti-nausea medications ● Swish mouth with water and spit out after treatment ● Eat a small meal prior to treatment
Fatigue	14.1% (n = 23)	<ul style="list-style-type: none"> ● Reevaluate for any clinical changes i.e., worsening volume status, oxygenation and/or disease progression
Diarrhea	13.5% (n = 22)	<ul style="list-style-type: none"> ● Evaluate other causes for fatigue ● Dietary - BRAT diet (Bananas, Rice, Applesauce, Toast) ● Anti-diarrheal agents
Throat irritation	12.3% (n = 20)	<ul style="list-style-type: none"> ● Oral phenol-based analgesic sprays (Chloraseptic) prior to treatment
Oropharyngeal pain	11.0% n (=18)	<ul style="list-style-type: none"> ● Drink warm or cold water prior to treatment ● Anti-inflammatory medication

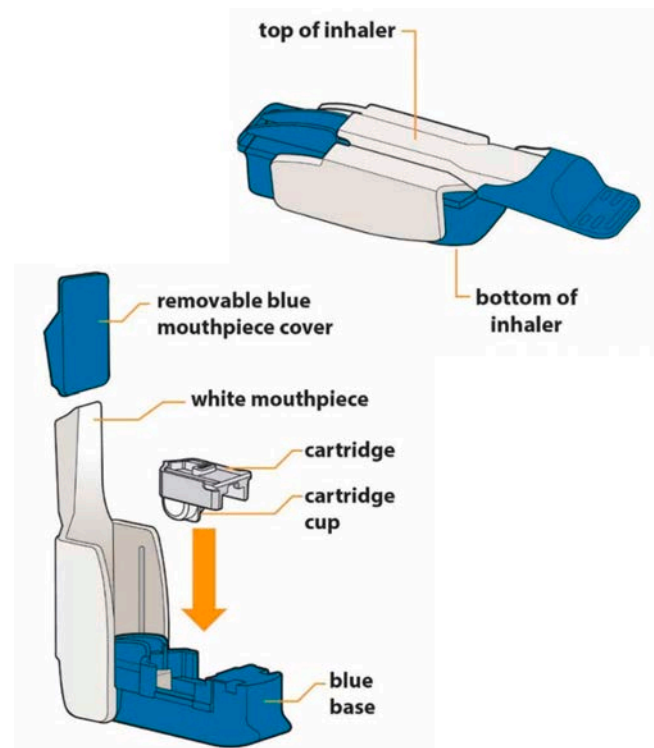


Fig. 4. Dry powder formulation of treprostinil and a small, portable, dry powder inhaler [26].

As new inhalation devices and therapies become available, providing the patient with resources and information in conjunction with an educated and engaged care team establishes the foundation critical to successful treatment.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence what is reported in this paper.

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EXHIBIT 12

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Olschewski et al.

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(43) **Pub. Date: Aug. 21, 2008**

(54) **TREPROSTINIL ADMINISTRATION USING A
 METERED DOSE INHALER**

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 514/250; 514/243; 514/269; 514/380; 514/469

(57) **ABSTRACT**

Treprostinil can be administered using a metered dose inhaler. Such administration provides a greater degree of autonomy to patients. Also disclosed are kits that include a metered dose inhaler containing a pharmaceutical formulation containing treprostinil.

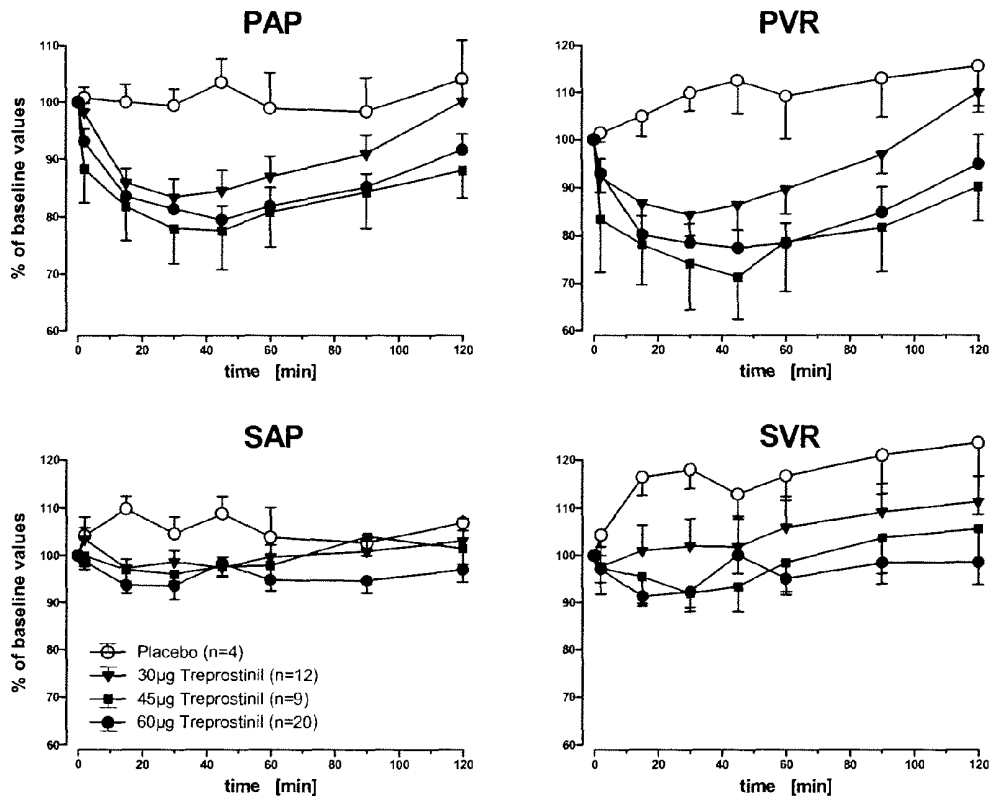


FIGURE 1

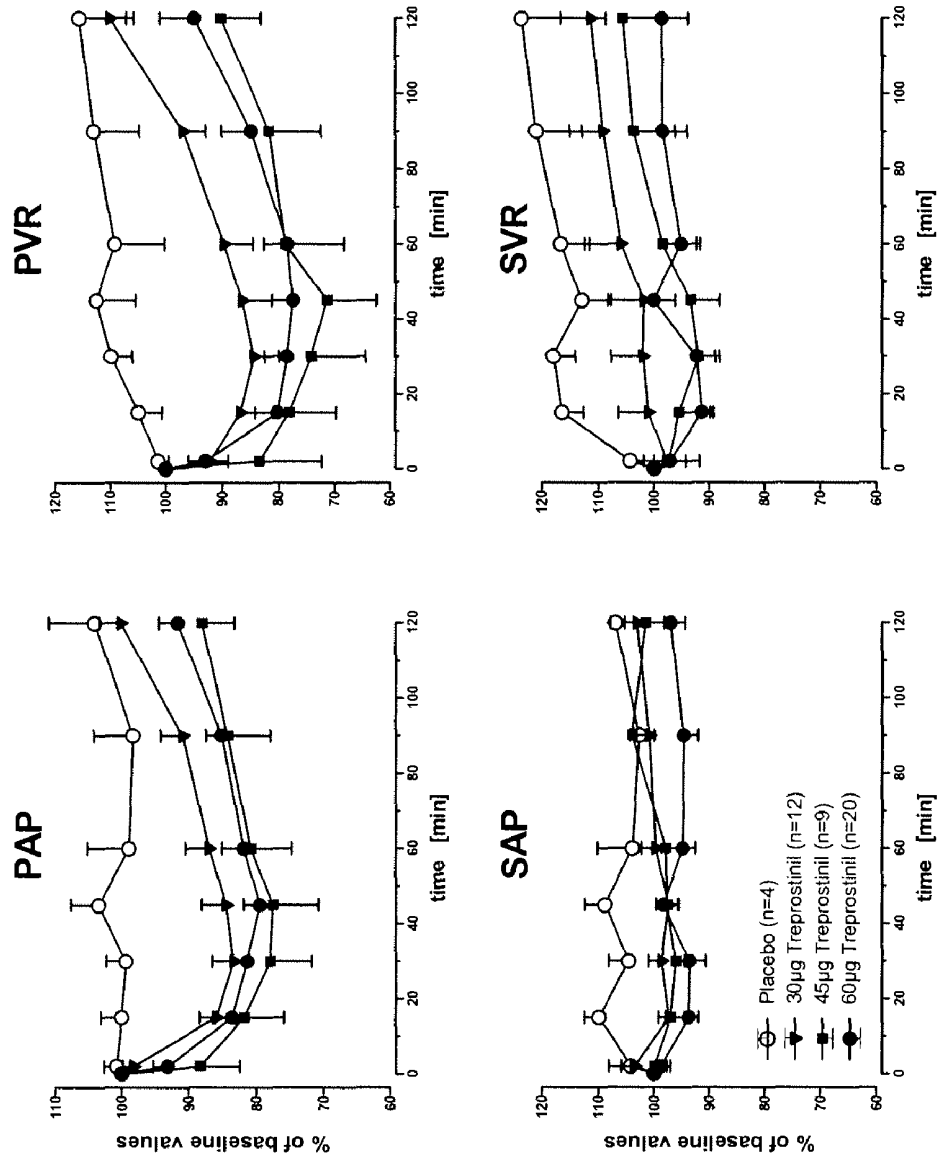


FIGURE 2

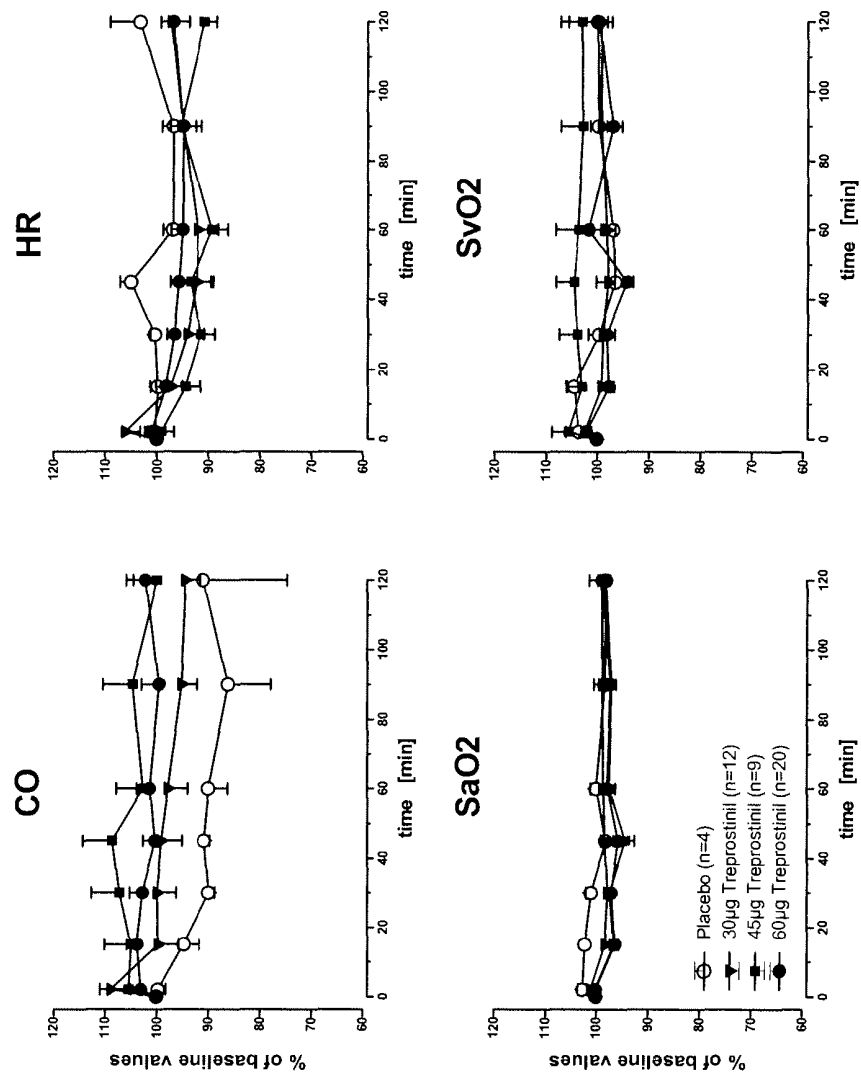


FIGURE 3

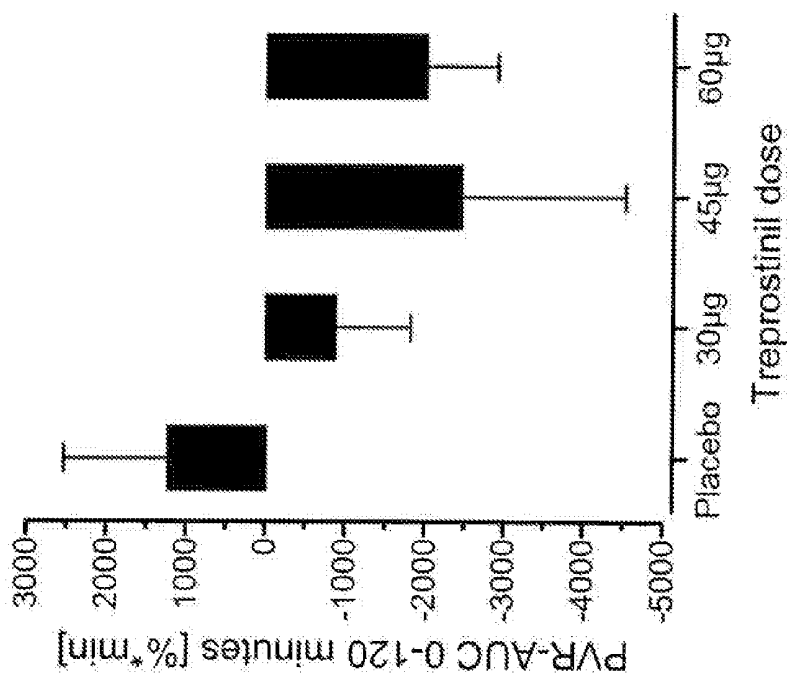


FIGURE 4

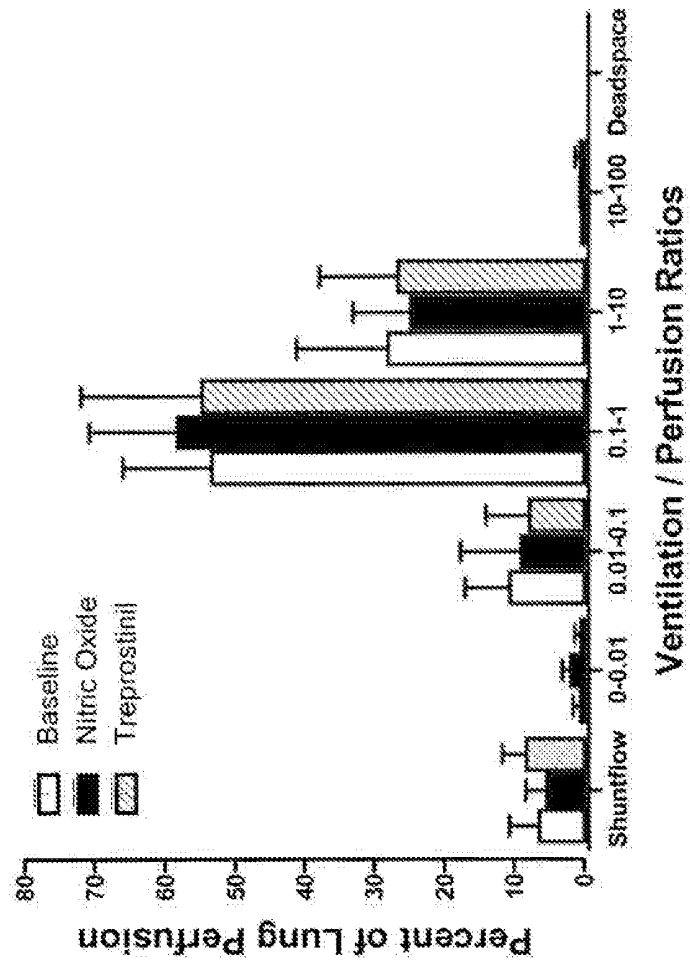


FIGURE 5

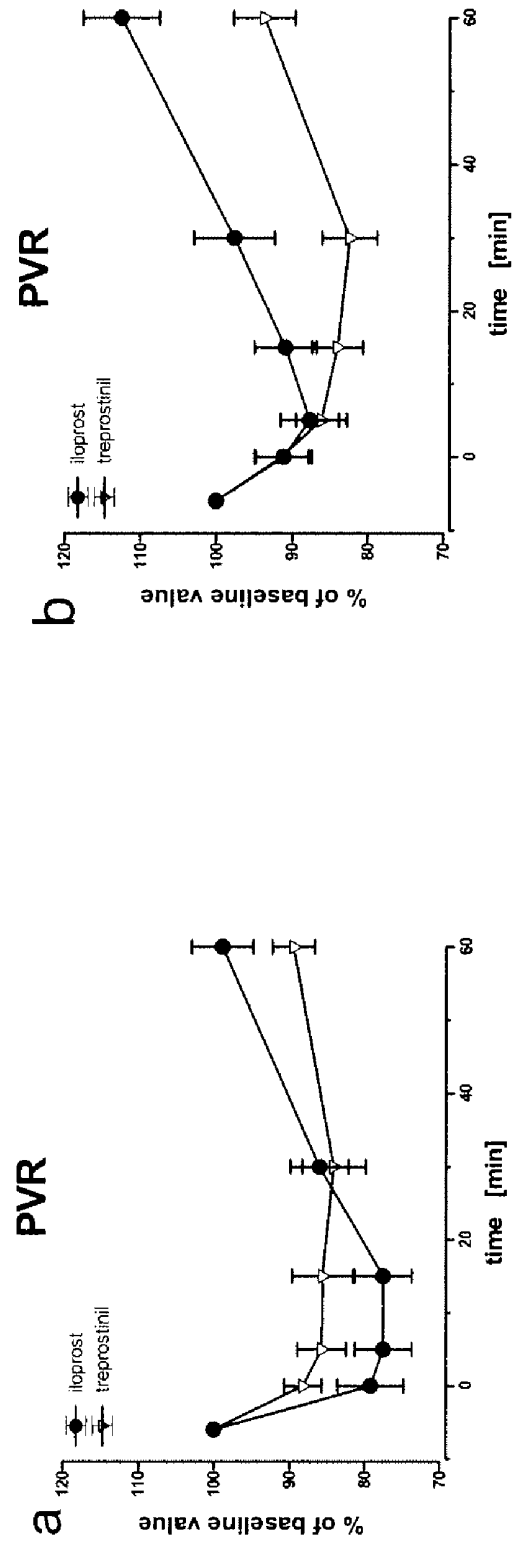


FIGURE 6

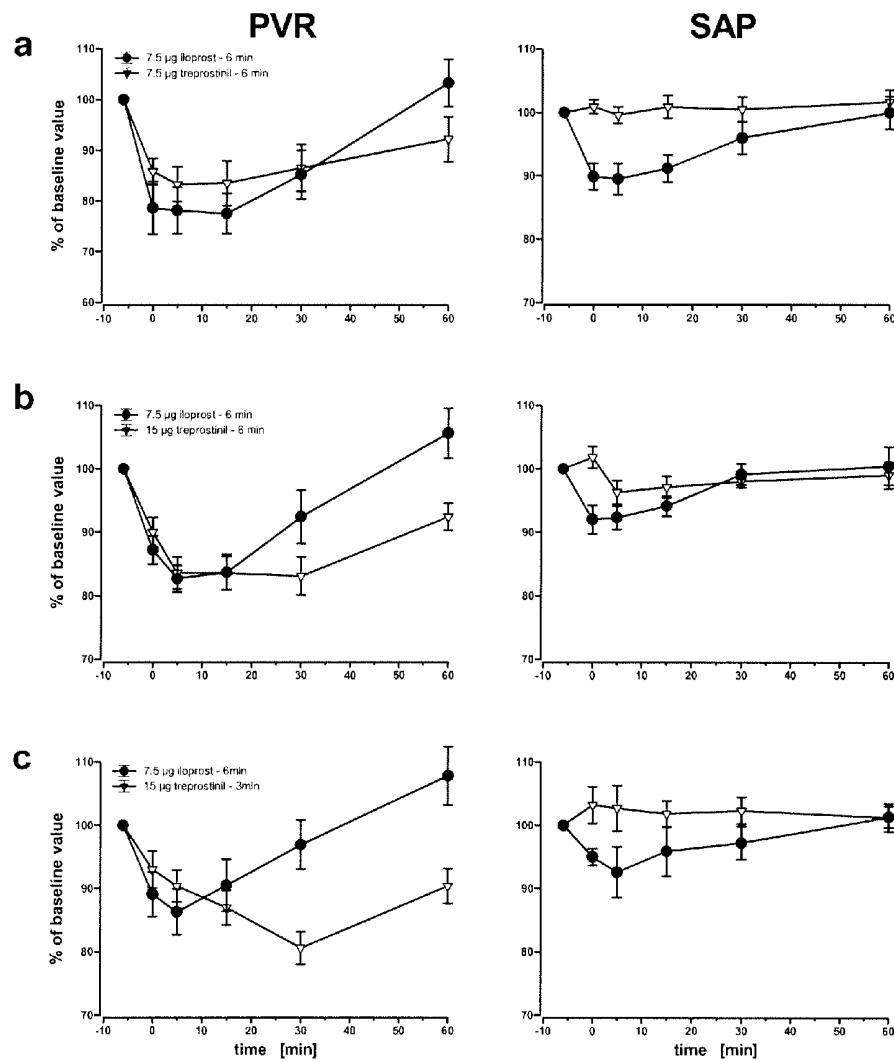


FIGURE 7

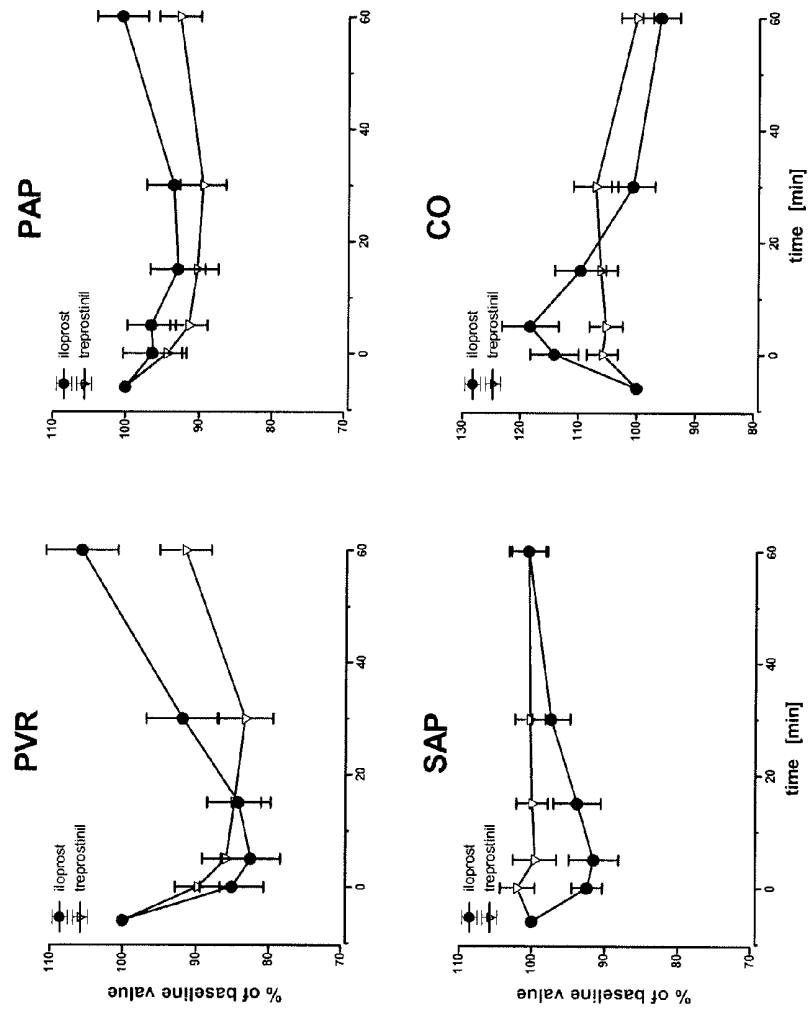


FIGURE 8

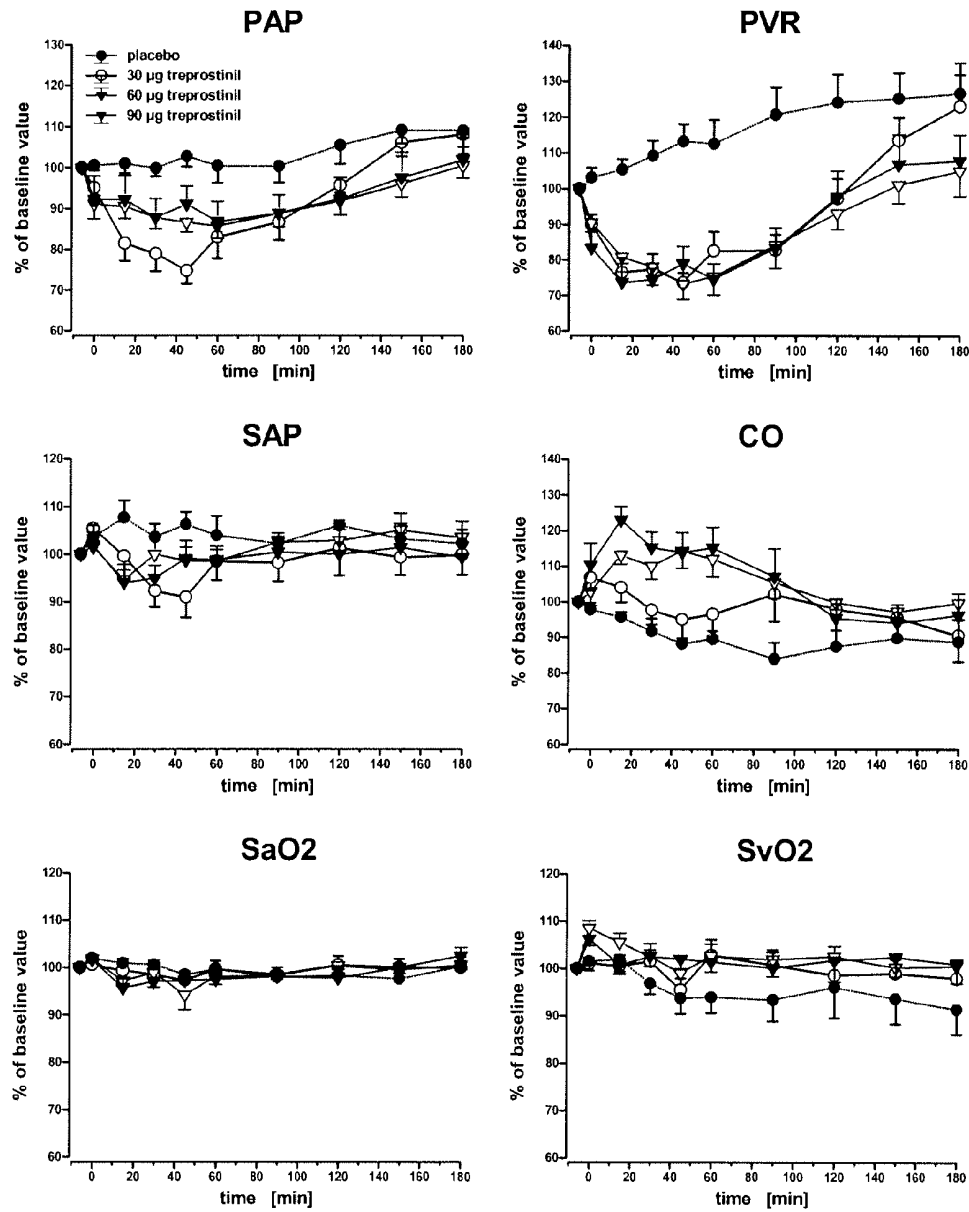


FIGURE 9

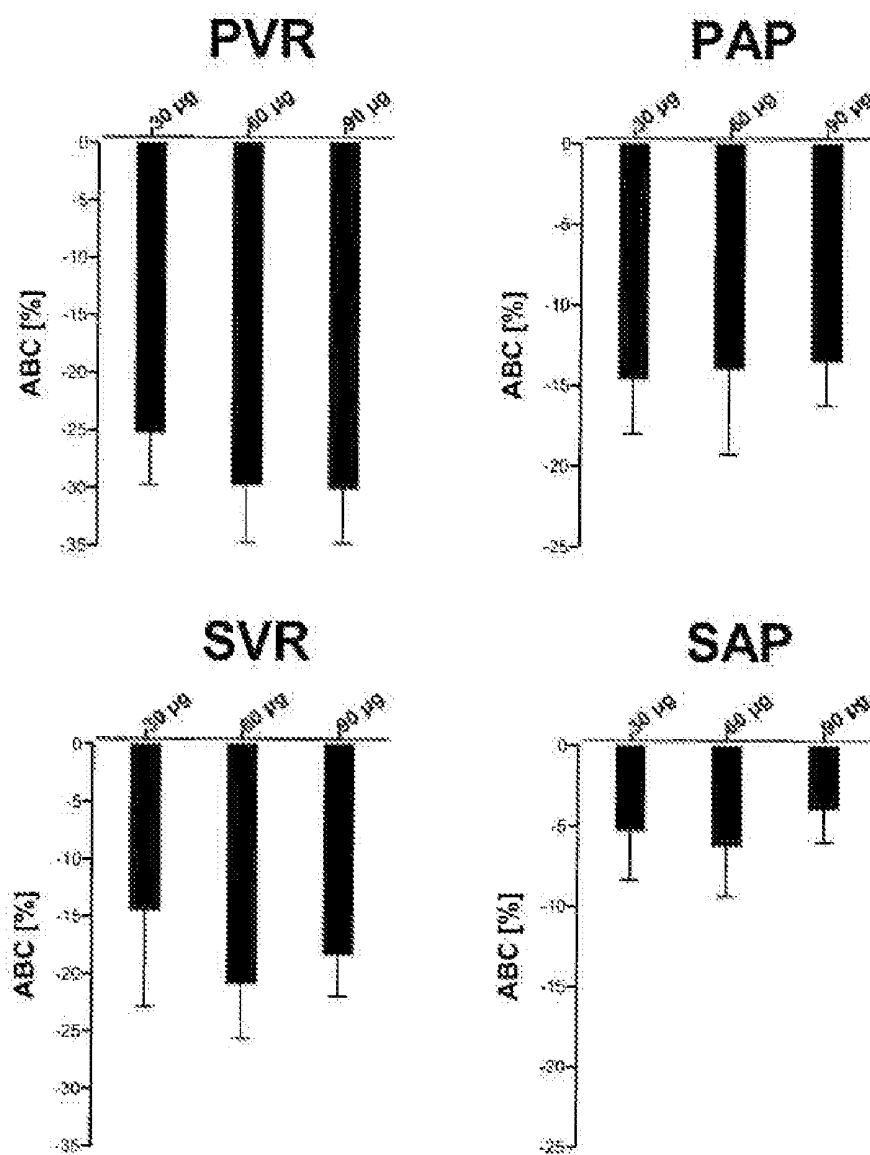


FIGURE 10

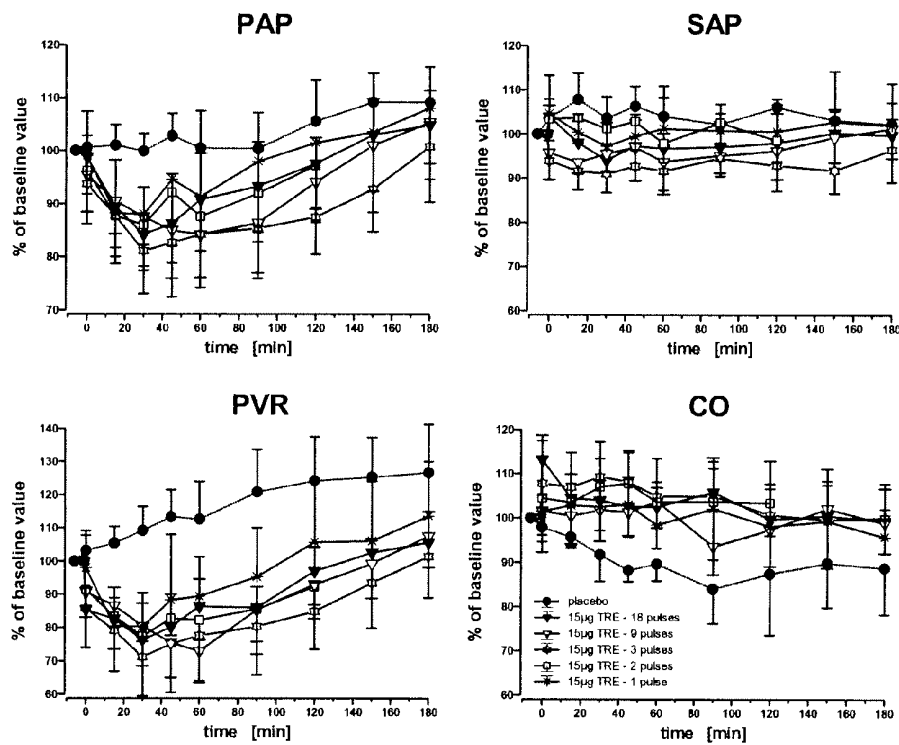


FIGURE 11

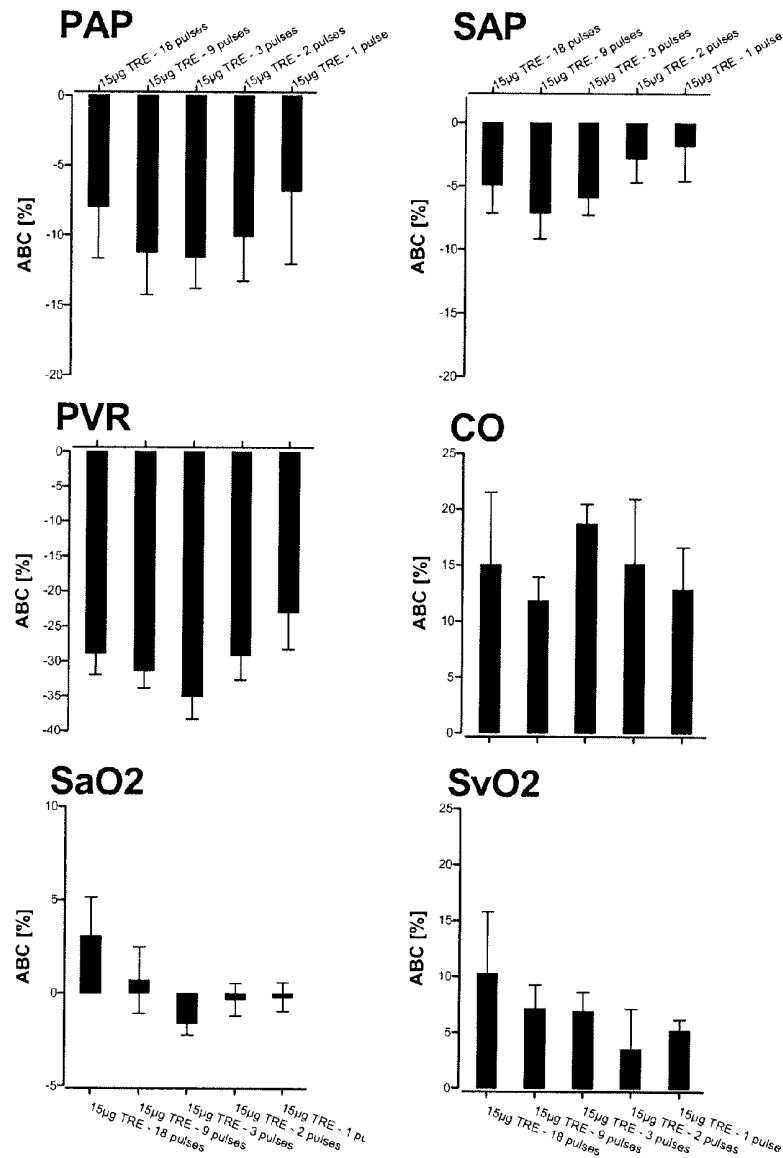
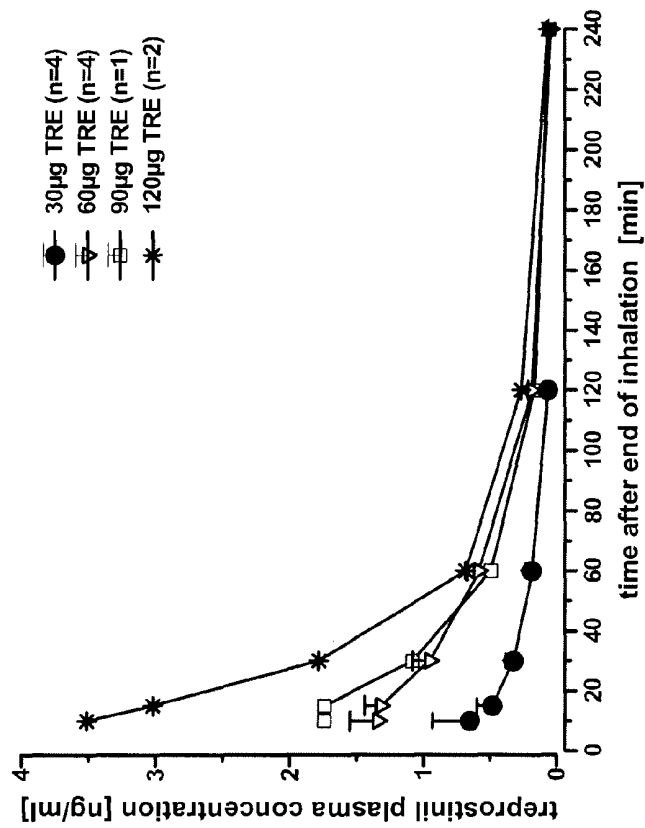


FIGURE 12



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TREPROSTINIL ADMINISTRATION USING A METERED DOSE INHALER

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims priority to U.S. provisional application No. 60/800,016 filed May 15, 2006, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present application relates to methods and kits for therapeutic treatment and, more particularly, to therapeutic methods involving administering treprostinil using a metered dose inhaler and related kits.

BACKGROUND OF THE INVENTION

[0003] All blood is driven through the lungs via the pulmonary circulation in order, among other things, to replenish the oxygen which it dispenses in its passage around the rest of the body via the systemic circulation. The flow through both circulations is in normal circumstances equal, but the resistance offered to it in the pulmonary circulation is generally much less than that of the systemic circulation. When the resistance to pulmonary blood flow increases, the pressure in the circulation is greater for any particular flow. The above described condition is referred to as pulmonary hypertension (PH). Generally, pulmonary hypertension is defined through observations of pressures above the normal range pertaining in the majority of people residing at the same altitude and engaged in similar activities.

[0004] Pulmonary hypertension may occur due to various reasons and the different entities of pulmonary hypertension were classified based on clinical and pathological grounds in 5 categories according to the latest WHO convention, see e.g. Simonneau G., et al. *J. Am. Coll. Cardiol.* 2004; 43(12 Suppl S):5S-12S. Pulmonary hypertension can be a manifestation of an obvious or explicable increase in resistance, such as obstruction to blood flow by pulmonary emboli, malfunction of the heart's valves or muscle in handling blood after its passage through the lungs, diminution in pulmonary vessel caliber as a reflex response to alveolar hypoxia due to lung diseases or high altitude, or a mismatch of vascular capacity and essential blood flow, such as shunting of blood in congenital abnormalities or surgical removal of lung tissue. In addition, certain infectious diseases, such as HIV and liver diseases with portal hypertension may cause pulmonary hypertension. Autoimmune disorders, such as collagen vascular diseases, also often lead to pulmonary vascular narrowing and contribute to a significant number of pulmonary hypertension patients. The cases of pulmonary hypertension remain where the cause of the increased resistance is as yet inexplicable are defined as idiopathic (primary) pulmonary hypertension (iPAH) and are diagnosed by and after exclusion of the causes of secondary pulmonary hypertension and are in the majority of cases related to a genetic mutation in the bone morphogenetic protein receptor-2 gene. The cases of idiopathic pulmonary arterial hypertension tend to comprise a recognizable entity of about 40% of patients cared for in large specialized pulmonary hypertension centers. Approximately 65% of the most commonly afflicted are female and young adults, though it has occurred in children and patients over 50. Life expectancy from the time of diagnosis is short without specific treatment, about 3 to 5 years, though occasional

reports of spontaneous remission and longer survival are to be expected given the nature of the diagnostic process. Generally, however, disease progress is inexorable via syncope and right heart failure and death is quite often sudden.

[0005] Pulmonary hypertension refers to a condition associated with an elevation of pulmonary arterial pressure (PAP) over normal levels. In humans, a typical mean PAP is approximately 12-15 mm Hg. Pulmonary hypertension, on the other hand, can be defined as mean PAP above 25 mmHg, assessed by right heart catheter measurement. Pulmonary arterial pressure may reach systemic pressure levels or even exceed these in severe forms of pulmonary hypertension. When the PAP markedly increases due to pulmonary venous congestion, i.e. in left heart failure or valve dysfunction, plasma can escape from the capillaries into the lung interstitium and alveoli. Fluid buildup in the lung (pulmonary edema) can result, with an associated decrease in lung function that can in some cases be fatal. Pulmonary edema, however, is not a feature of even severe pulmonary hypertension due to pulmonary vascular changes in all other entities of this disease.

[0006] Pulmonary hypertension may either be acute or chronic. Acute pulmonary hypertension is often a potentially reversible phenomenon generally attributable to constriction of the smooth muscle of the pulmonary blood vessels, which may be triggered by such conditions as hypoxia (as in high-altitude sickness), acidosis, inflammation, or pulmonary embolism. Chronic pulmonary hypertension is characterized by major structural changes in the pulmonary vasculature, which result in a decreased cross-sectional area of the pulmonary blood vessels. This may be caused by, for example, chronic hypoxia, thromboembolism, collagen vascular diseases, pulmonary hypercirculation due to left-to-right shunt, HIV infection, portal hypertension or a combination of genetic mutation and unknown causes as in idiopathic pulmonary arterial hypertension.

[0007] Pulmonary hypertension has been implicated in several life-threatening clinical conditions, such as adult respiratory distress syndrome ("ARDS") and persistent pulmonary hypertension of the newborn ("PPHN"). Zapol et al., *Acute Respiratory Failure*, p. 241-273, Marcel Dekker, New York (1985); Peckham, *J. Ped.* 93:1005 (1978). PPHN, a disorder that primarily affects full-term infants, is characterized by elevated pulmonary vascular resistance, pulmonary arterial hypertension, and right-to-left shunting of blood through the patent ductus arteriosus and foramen ovale of the newborn's heart. Mortality rates range from 12-50%. Fox, *Pediatrics* 59:205 (1977); Dworetz, *Pediatrics* 84:1 (1989). Pulmonary hypertension may also ultimately result in a potentially fatal heart condition known as "cor pulmonale," or pulmonary heart disease. Fishman, *"Pulmonary Diseases and Disorders"* 2nd Ed., McGraw-Hill, New York (1988).

[0008] Currently, there is no treatment for pulmonary hypertension that can be administered using a compact inhalation device, such as a metered dose inhaler.

SUMMARY OF THE INVENTION

[0009] One embodiment is a method of delivering to a subject in need thereof a therapeutically effective amount of treprostinil, or treprostinil derivative or a pharmaceutically acceptable salt thereof comprising administering to the subject a therapeutically effective amount of the treprostinil or treprostinil derivative or a pharmaceutically acceptable salt thereof using a metered dose inhaler.

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[0010] Another embodiment is a method for treating pulmonary hypertension comprising administering to a subject in need thereof treprostinil or its derivative, or a pharmaceutically acceptable salt thereof using a metered dose inhaler.

[0011] Yet another embodiment is a kit comprising a metered dose inhaler containing a pharmaceutical formulation comprising treprostinil or treprostinil derivative, or a pharmaceutically acceptable salt thereof.

[0012] And yet another embodiment is a kit for treating pulmonary hypertension in a subject, comprising (i) an effective amount of treprostinil or its derivative, or a pharmaceutically acceptable salt thereof, (ii) a metered dose inhaler; (iii) instructions for use in treating pulmonary hypertension.

[0013] Administration of treprostinil using a metered dose inhaler can provide patients, such as pulmonary hypertension patients, with a high degree of autonomy.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] FIG. 1 pulmonary and systemic changes in hemodynamics following the inhalation of placebo (open circles), 30 µg treprostinil (triangles), 45 µg treprostinil (squares) or 60 µg TREprostinil (black circles) applied by a Metered Dose Inhaler (MDI-TRE). A single short inhalation of treprostinil induced sustained reduction of PAP and PVR that outlasted the observation period of 120 minutes at doses of 45 and 60 µg MDI-TRE. Systemic arterial pressure and resistance were not significantly affected. PAP=mean pulmonary artery pressure; PVR=pulmonary vascular resistance; SAP=mean systemic arterial pressure; SVR=systemic vascular resistance. Data are given as mean value±standard error of the mean (SEM).

[0015] FIG. 2 presents hemodynamic changes induced by the inhalation of placebo (open circles), 30 µg treprostinil (triangles), 45 µg treprostinil (squares) or 60 µg treprostinil (black circles) applied by a metered dose inhaler. Treprostinil induced sustained elevation of cardiac output. Heart rate was rather unchanged as a sign for low spillover of MDI-TRE to the systemic circulation. Gas exchange was not negatively affected. CO=cardiac output; HR=heart rate; SaO₂=arterial oxygen saturation; SvO₂=central venous oxygen saturation. Data are given as mean value±SEM.

[0016] FIG. 3 shows areas under the curve for changes in pulmonary vascular resistance (PVR) calculated for an observation period of 120 minutes after inhalation treprostinil using a metered dose inhaler. PVR was markedly lowered by treprostinil inhalation. The increased pulmonary vasodilation over time with the two highest doses mainly relies on the more sustained effect over time. Data are shown as mean value±95% confidence intervals.

[0017] FIG. 4 demonstrates Ventilation-perfusion matching measured with the multiple inert gas elimination technique. Five patients (30 µg TRE, n=2; 45 µg TRE, n=1; 60 µg TRE, n=2) with pre-existing gas exchange problems were investigated for changes in ventilation-perfusion ratios. All patients had significant shunt flow at baseline. Shunt-flow and low V/Q areas were not significantly changed by nitric oxide (NO) inhalation or treprostinil inhalation using a metered dose inhaler (MDI-TRE). MDI-TRE applied at high treprostinil concentrations did not negatively affect ventilation-perfusion matching and gas-exchange. Data are given as mean value±95% confidence intervals.

[0018] FIG. 5 presents response of pulmonary vascular resistance (PVR) to inhaled treprostinil vs. iloprost—period effects. a) First inhalation with treprostinil (n=22) vs. first inhalation with iloprost (n=22); b) second inhalation with

treprostinil (n=22) vs. second inhalation with iloprost (n=22). The PVR decrease with treprostinil was delayed and prolonged, compared to iloprost. Due to carryover effects from the first period, in the second period, the effects of both drugs appeared shortened. Data are shown as percent of baseline values (mean value±95% confidence interval).

[0019] FIG. 6 presents response of PVR and systemic arterial pressure (SAP) to inhalation of treprostinil vs. iloprost—dose effects. a) Inhalation of 7.5 µg iloprost (in 6 min) vs. 7.5 µg treprostinil (6 min) (n=14, in a randomized order). b) Inhalation of 7.5 µg iloprost (6 min) vs. 15 µg treprostinil (6 min) (n=14, in randomized order). c) Inhalation of 7.5 µg iloprost (6 min) vs. 15 µg treprostinil (3 min) (n=16, in randomized order). Data are shown as percent of baseline values (mean±95% confidence interval). Iloprost, filled circles; Treprostinil, open triangles.

[0020] FIG. 7 presents hemodynamic response to inhalation of treprostinil vs. iloprost. Data from n=44 patients, who inhaled both drugs in randomized order, shown as percent of baseline values (mean value±95% confidence interval). PVR, pulmonary vascular resistance; PAP, mean pulmonary arterial pressure; SAP, mean systemic arterial pressure; CO, cardiac output.

[0021] FIG. 8 presents pharmacodynamics after treprostinil inhalation vs. placebo. Placebo or treprostinil in doses of 30 µg, 60 µg or 90 µg were inhaled (means±95% confidence intervals). Maximal decrease of PVR was comparable for all doses. The duration of pulmonary vasodilation (PVR-decrease) appeared to be dose dependent. PVR, pulmonary vascular resistance; PAP, mean pulmonary arterial pressure; SAP, mean systemic arterial pressure; CO, cardiac output; SaO₂, arterial oxygen saturation; SvO₂, mixed venous oxygen saturation.

[0022] FIG. 9 presents Areas Between the placebo and the treprostinil Curves (ABC). ABCs were calculated for a 3-hour period after inhalation of TRE or placebo from the relative changes of hemodynamic parameters (means±95% confidence intervals). PVR, pulmonary vascular resistance; PAP, mean pulmonary arterial pressure; SAP, mean systemic arterial pressure; SVR, systemic vascular resistance.

[0023] FIG. 10 presents hemodynamic responses to the inhalation of 15 µg treprostinil. The inhalation time by increasing treprostinil concentration. A pulse of aerosol was generated every 6 seconds. TRE aerosol was inhaled in concentrations of 100 µg/ml (18 pulses; n=6), 200 µg/ml (9 pulses; n=6), 600 µg/ml (3 pulses; n=21), 1000 µg/ml (2 pulses; n=7) and 2000 µg/ml (1 pulse; n=8). Placebo data correspond to FIG. 8. Data are shown as means±95% confidence intervals. PVR, pulmonary vascular resistance; PAP, mean pulmonary arterial pressure; SAP, mean systemic arterial pressure; CO, cardiac output.

[0024] FIG. 11 presents areas between the placebo curve and the responses to 15 µg treprostinil applied at increasing concentrations to minimize inhalation time. Mean±SEM of relative changes of hemodynamic parameters (observation time 120 min). PAP, pulmonary arterial pressure, SAP, systemic arterial pressure, PVR, pulmonary vascular resistance, CO, cardiac output, SaO₂, systemic arterial oxygen saturation, SvO₂, pulmonary arterial oxygen saturation.

[0025] FIG. 12 presents pharmacokinetics of treprostinil after a single inhalation. Treprostinil plasma levels after inhalation of 30 µg, 60 µg, 90 µg or 120 µg treprostinil (6 min

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inhalation period; experiments correspond to those shown in FIGS. 8 and 9). Data with error bars represent mean values \pm SEM.

DETAILED DESCRIPTION OF THE INVENTION

[0026] Unless otherwise specified, the term “a” or “an” used herein shall mean “one or more.”

[0027] The present application incorporates herein by reference in its entirety Voswinkel R, et al. J. Am. Coll. Cardiol. 2006; 48:1672-1681.

[0028] The inventors discovered that a therapeutically effective dose of treprostinil can be administered in a few single inhalations using a compact inhalation device, such as a metered dose inhaler. Furthermore, the inventors discovered that such administering does not cause significant side effects, especially no significant side effects related to systemic blood pressure and circulation as well as no gas exchange deteriorations or disruptions.

[0029] Accordingly, one embodiment of the invention is a method of delivering to a subject in need thereof, such as a human being, a therapeutically effective amount of treprostinil comprising administering to the subject a formulation comprising a therapeutically effective amount of treprostinil, its derivative or a pharmaceutically acceptable salt thereof using a metered dose inhaler. Treprostinil can be administered via a metered dose inhaler to a subject affected with a condition or disease, which can be treated by treprostinil, such as asthma, pulmonary hypertension, peripheral vascular disease or pulmonary fibrosis.

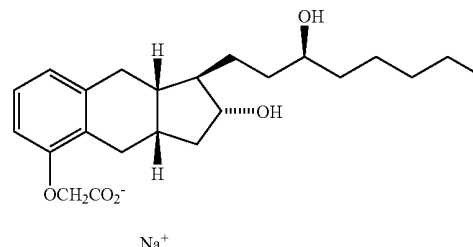
[0030] Another embodiment of the invention is a method for treating pulmonary hypertension, comprising administering to a subject in need thereof, such as a human being, treprostinil or its derivative, or a pharmaceutically acceptable salt using a metered dose inhaler.

[0031] Treprostinil, or 9-deoxy-2',9- α -methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)-13,14-dihydro-prostaglandin F₁, is a prostacyclin analogue, first described in U.S. Pat. No. 4,306,075. U.S. Pat. No. 5,153,222 describes use of treprostinil for treatment of pulmonary hypertension. Treprostinil is approved for the intravenous as well as subcutaneous route, the latter avoiding septic events associated with continuous intravenous catheters. U.S. Pat. Nos. 6,521,212 and 6,756,033 describe administration of treprostinil by inhalation for treatment of pulmonary hypertension, peripheral vascular disease and other diseases and conditions. U.S. Pat. No. 6,803,386 discloses administration of treprostinil for treating cancer such as lung, liver, brain, pancreatic, kidney, prostate, breast, colon and head-neck cancer. US patent application publication No. 2005/0165111 discloses treprostinil treatment of ischemic lesions. U.S. Pat. No. 7,199,157 discloses that treprostinil treatment improves kidney functions. US patent application publication No. 2005/0282903 discloses treprostinil treatment of neuropathic foot ulcers. U.S. provisional application No. 60/900,320 filed Feb. 9, 2007, discloses treprostinil treatment of pulmonary fibrosis.

[0032] The term “acid derivative” is used herein to describe C1-4 alkyl esters and amides, including amides wherein the nitrogen is optionally substituted by one or two C1-4 alkyl groups.

[0033] The present invention also encompasses methods of using Treprostinil or its derivatives, or pharmaceutically acceptable salts thereof. In one embodiment, a method uses Treprostinil sodium, currently marketed under the trade name of REMODULIN®. The FDA has approved Treprostinil

sodium for the treatment of pulmonary arterial hypertension by injection of dose concentrations of 1.0 mg/mL, 2.5 mg/mL, 5.0 mg/mL and 10.0 mg/mL. The chemical structure formula for Treprostinil sodium is:



[0034] Treprostinil sodium is sometimes designated by the chemical names: (a) [(1R,2R,3aS,9aS)-2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]acetic acid; or (b) 9-deoxy-2',9- α -methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)-13,14-dihydro-prostaglandin F₁. Treprostinil sodium is also known as: UT-15; LRX-15; 15AU81; UNIPROST™; BW A15AU; and U-62,840. The molecular weight of Treprostinil sodium is 390.52, and its empirical formula is C₂₃H₃₄O₅.

[0035] In certain embodiments, treprostinil can be administered in combination with one or more additional active agents. In some embodiments, such one or more additional active agents can be also administered together with treprostinil using a metered dose inhaler. Yet in some embodiments, such one or more additional active agents can be administered separately from treprostinil. Particular additional active agents that can be administered in combination with treprostinil may depend on a particular disease or condition for treatment or prevention of which treprostinil is administered. In some cases, the additional active agent can be a cardiovascular agent such as a calcium channel blocker, a phosphodiesterase inhibitor, an endothelial antagonist, or an antiplatelet agent.

[0036] The present invention extends to methods of using physiologically acceptable salts of Treprostinil, as well as non-physiologically acceptable salts of Treprostinil that may be used in the preparation of the pharmacologically active compounds of the invention.

[0037] The term “pharmaceutically acceptable salt” refers to a salt of Treprostinil with an inorganic base, organic base, inorganic acid, organic acid, or basic or acidic amino acid. Salts of inorganic bases can be, for example, salts of alkali metals such as sodium or potassium; alkaline earth metals such as calcium and magnesium or aluminum; and ammonia. Salts of organic bases can be, for example, salts trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, and triethanolamine. Salts of inorganic acids can be, for example, salts of hydrochloric acid, hydroboric acid, nitric acid, sulfuric acid, and phosphoric acid. Salts of organic acids can be, for example, salts of formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, lactic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, and p-toluenesulfonic acid. Salts of basic amino acids can be, for example, salts of arginine, lysine and ornithine. Salts of acidic amino acids can include, for example, salts of aspartic acid and glutamic acid. Quaternary ammonium salts can be

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formed, for example, by reaction with lower alkyl halides, such as methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides, with dialkyl sulphates, with long chain halides, such as decyl, lauryl, myristyl, and stearyl chlorides, bromides, and iodides, and with aralkyl halides, such as benzyl and phenethyl bromides.

[0038] Preferred pharmaceutically acceptable salts are disclosed, for example, in US patent application publication No. 20050085540.

[0039] Treprostinil can be administered by inhalation, which in the present context refers to the delivery of the active ingredient or a combination of active ingredients through a respiratory passage, wherein the subject in need of the active ingredient(s) through the subject's airways, such as the subject's nose or mouth.

[0040] A metered dose inhaler in the present context means a device capable of delivering a metered or bolus dose of respiratory drug, such as treprostinil, to the lungs. One example of the inhalation device can be a pressurized metered dose inhaler, a device which produces the aerosol clouds for inhalation from solutions and/or suspensions of respiratory drugs in chlorofluorocarbon (CFC) and/or hydrofluoroalkane (HFA) solutions.

[0041] The inhalation device can be also a dry powder inhaler. In such case, the respiratory drug is inhaled in solid formulation, usually in the form of a powder with particle size less than 10 micrometers in diameter or less than 5 micrometers in diameter.

[0042] The metered dose inhaler can be a soft mist inhaler (SMI), in which the aerosol cloud containing a respiratory drug can be generated by passing a solution containing the respiratory drug through a nozzle or series of nozzles. The aerosol generation can be achieved in SMI, for example, by mechanical, electromechanical or thermomechanical process. Examples of soft mist inhalers include the RespiMat® Inhaler (Boehringer Ingelheim GmbH), the AERx® Inhaler (Aradigm Corp.), the Mystic™ Inhaler (Ventaira Pharmaceuticals, Inc) and the Aira™ Inhaler (Chrysalis Technologies Incorporated). For a review of soft mist inhaler technology, see e.g. M. Hindle, The Drug Delivery Companies Report, Autumn/Winter 2004, pp. 31-34. The aerosol for SMI can be generated from a solution of the respiratory drug further containing pharmaceutically acceptable excipients. In the present case, the respiratory drug is treprostinil, its derivative or a pharmaceutically acceptable salt thereof, which can be formulated in SMI as a solution. The solution can be, for example, a solution of treprostinil in water, ethanol or a mixture thereof. Preferably, the diameter of the treprostinil-containing aerosol particles is less than about 10 microns, or less than about 5 microns, or less than about 4 microns.

[0043] Treprostinil concentration in an aerosolable formulation, such as a solution, used in a metered dose inhaler can range from about 500 µg/ml to about 2500 µg/ml, or from about 800 µg/ml to about 2200 µg/ml, or from about 1000 µg/ml to about 2000 µg/ml.

[0044] The dose of treprostinil that can be administered using a metered dose inhaler in a single event can be from about 15 µg to about 100 µg or from about 15 µg to about 90 µg or from about 30 µg to about 90 µg or from about 30 µg to about 60 µg.

[0045] Administering of treprostinil in a single event can be carried out in a limited number of breaths by a patient. For example, treprostinil can be administered in 20 breaths or

less, or in 10 breaths or less, or than 5 breaths or less. Preferably, treprostinil is administered in 3, 2 or 1 breaths.

[0046] The total time of a single administering event can be less than 5 minutes, or less than 1 minute, or less than 30 seconds.

[0047] Treprostinil can be administered a single time per day or several times per day.

[0048] In some embodiments, the method of treatment of pulmonary hypertension can further comprise administering at least one supplementary agent selected from the group consisting of sildenafil, tadalafil, calcium channel blockers (diltiazem, amlodipine, nifedipine), bosentan, sitaxsentan, ambrisentan, and pharmaceutically acceptable salts thereof. In some embodiments, the supplementary agents can be included in the treprostinil formulation and, thus, can be administered simultaneously with treprostinil using a metered dose inhaler. In some embodiments, the supplementary agents can be administered separately from treprostinil. In some embodiments, the application of intravenous prostacyclin (flolan), intravenous iloprost or intravenous or subcutaneous treprostinil can be administered in addition to treprostinil administered via inhalation using a metered dose inhaler.

[0049] The present invention also provides a kit that includes a metered dose inhaler containing a pharmaceutical formulation comprising treprostinil or its derivative, or a pharmaceutically acceptable salt thereof. Such a kit can further include instructions on how to use the metered dose inhaler for inhaling treprostinil. Such instructions can include, for example, information on how to coordinate patient's breathing, and actuation of the inhaler. The kit can be used by a subject, such as human being, affected with a disease or condition that can be treated by treprostinil, such as asthma, pulmonary hypertension, peripheral vascular disease or pulmonary fibrosis.

[0050] In some cases, the kit is a kit for treating pulmonary hypertension, that includes (i) a metered dose inhaler containing a pharmaceutical formulation comprising treprostinil or its derivative, or a pharmaceutically acceptable salt thereof, and (ii) instructions for use of the metered dose inhaler containing treprostinil in treating pulmonary hypertension.

[0051] As used herein, the phrase "instructions for use" shall mean any FDA-mandated labeling, instructions, or package inserts that relate to the administration of Treprostinil or its derivatives, or pharmaceutically acceptable salts thereof, for treatment of pulmonary hypertension by inhalation. For example, instructions for use may include, but are not limited to, indications for pulmonary hypertension, identification of specific symptoms associated with pulmonary hypertension, that can be ameliorated by Treprostinil, recommended dosage amounts for subjects suffering from pulmonary hypertension and instructions on coordination of individual's breathing and actuation of the metered dose inhaler.

[0052] The present invention can be illustrated in more detail by the following example, however, it should be understood that the present invention is not limited thereto.

EXAMPLE 1

Open Label Study upon Acute Safety, Tolerability and Hemodynamic Effects of Inhaled Treprostinil Delivered in Seconds

[0053] A study was conducted of acute vasodilator challenge during right heart catheter investigation to determine

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the safety, tolerability and pulmonary vasodilatory potency of inhaled treprostinil applied in seconds by a soft mist inhaler (SMI-TRE). The study produced evidence for a long lasting favourable effect of SMI-TRE on pulmonary hemodynamics in absence of systemic side effects and gas exchange disruptions.

Summary:

[0054] Inhaled nitric oxide (20 ppm; n=45) and inhaled treprostinil sodium (TRE; n=41) or placebo (n=4) were applied once during right heart catheter investigation. TRE was delivered in 2 breaths (1000 µg/ml aerosol concentration; 30 µg dose; n=12), 3 breaths (1000 µg/ml; 45 µg; n=9) or 2 breaths (2000 µg/ml; 60 µg; n=20) from a Respimat® SMI. Pulmonary hemodynamics and blood gases were measured at defined time points, observation time following TRE application was 120 minutes. TRE doses of 30 µg, 45 µg and 60 µg reduced pulmonary vascular resistance (PVR) to 84.4±8.7%, 71.4±17.5% and 77.5±7.2% of baseline values, respectively (mean±95% confidence interval). The 120 minute area under the curve for PVR for placebo, 30 µg, 45 µg and 60 µg TRE was 1230±1310, -870±940, -2450±2070 and -2000±900 min %, respectively. Reduction of PVR by a single inhalation of the two higher doses outlasted the observation period of 120 minutes. Reduction of systemic vascular resistance and pressure was negligible, showing a high pulmonary selectivity for SMI-TRE. Intrapulmonary selectivity was also provided by SMI-TRE as ventilation/perfusion matching, assessed by the multiple inert gas elimination technique in 5 patients with gas exchange problems, was not significantly different after SMI-TRE compared to inhaled nitric oxide or no treatment. No significant side effects were observed.

[0055] Conclusions: The acute application of inhaled treprostinil with a metered dose inhaler in 2-3 breaths was safe, well tolerated and induced a strong and sustained pulmonary selective vasodilation.

Methods and Patients

[0056] A total number of 45 patients with moderate to severe precapillary pulmonary hypertension were enrolled. Patient characteristics were: female to male ratio (f/m)=29/16, age 59±2.3 years, pulmonary artery pressure (PAP) 45±1.8 mmHg, pulmonary vascular resistance (PVR) 743±52 dynes·s·cm⁻⁵, pulmonary artery wedge pressure (PAWP) 8.6±0.5 mmHg, central venous pressure (CVP) 6.4±0.7 mmHg, cardiac output (CO) 4.5±0.2 l/min, central venous oxygen saturation (SvO2) 62.3±1.2 mmHg (mean±Standard Error of the Mean). Disease etiologies were idiopathic PAH (iPAH) (n=13), PAH other (n=11), chronic thromboembolic pulmonary hypertension (CTEPH) (n=17) and pulmonary fibrosis (n=4). Table 1 presents the patient characteristics of the different groups.

TABLE 1

Patient characteristics of the different treatment groups.				
	Placebo (n = 4)	30 µg TRE (n = 12)	45 µg TRE (n = 9)	60 µg TRE (n = 20)
Age [years]	61 ± 8	53.9 ± 3.9	54.2 ± 5.7	65.5 ± 3.1
PAP [mmHg]	49.5 ± 10.1	45 ± 3.1	54.3 ± 2.8	39.7 ± 2.0
PVR [Dynes]	896 ± 163	597 ± 53.9	1049 ± 107	663 ± 81
CO [l/min]	4.46 ± 0.9	5.2 ± 0.4	3.9 ± 0.4	4.4 ± 0.3
SAP [mmHg]	98 ± 8.1	90.1 ± 3.2	82.8 ± 3.9	86.1 ± 2.0

TABLE 1-continued

Patient characteristics of the different treatment groups.				
	Placebo (n = 4)	30 µg TRE (n = 12)	45 µg TRE (n = 9)	60 µg TRE (n = 20)
SaO2 [%]	85.3 ± 4.5	90.0 ± 1.1	89.6 ± 1.1	90.6 ± 0.5
SvO2 [%]	57.5 ± 3.9	66.0 ± 1.6	59.1 ± 3.4	62.5 ± 1.6

Data are given as mean ± Standard Error of the Mean (SEM).

PAP = pulmonary artery pressure;

PVR = pulmonary vascular resistance;

CO = cardiac output;

SAP = systemic arterial pressure;

SaO2 = arterial oxygen saturation;

SvO2 = central venous oxygen saturation.

[0057] Baseline values were determined 20-30 minutes after placement of the catheter. Heart rate, pulmonary and systemic blood pressure and cardiac output were measured and blood gases were taken during each pharmacological intervention at defined time points. Pharmacological interventions included the inhalation of 20 ppm nitric oxide (NO) after evaluation of baseline parameters (n=45) and the consecutive inhalation of placebo (n=4), 30 µg SMI-TRE (n=12), 45 µg SMI-TRE (n=9) or 60 µg (n=20) SMI-TRE. Placebo and treprostinil was applied with the Respimat® SMI. For filling of this device with treprostinil sodium, the placebo solution was withdrawn from the device with a syringe and treprostinil solution was injected into the device under sterile conditions. Aerosol quality was controlled before and after refilling of the SMI devices by laser diffractometry, see e.g. Gessler T., Schmehl T., Hoepfer M. M., Rose F., Ghofrani H. A., Olschewski H. et al. Ultrasonic versus jet nebulization of iloprost in severe pulmonary hypertension. Eur. Respir. J. 2001; 17:14-19 incorporated herein in its entirety. The aerosol sizes before (placebo) and after filling (treprostinil) were unchanged. The aerosol particles mass median aerodynamic diameter of treprostinil-aerosol was 4-5 µm, which can be at the upper limit for alveolar deposition. The aerosol volume delivered by one cycle from the SMI was 15 µl. The solution used for aerosol generation was prepared from treprostinil sodium salt using a standard protocol. The SMI was either filled with a concentration of 1000 µg/ml treprostinil sodium (one aerosol puff=15 µg TRE) or with 2000 µg/ml (one puff=30 µg TRE). The different doses were applied as 2 puffs 1000 µg/ml (30 µg), 3 puffs 1000 µg/ml (45 µg) and 2 puffs 2000 µg/ml (60 µg). The placebo was inhaled as 2 puffs from a placebo-SMI. Hemodynamics and gas-exchange parameters were recorded for 120 minutes after TRE inhalation. This study used the Respimat® device, because the implemented "soft mist" technology was well suited for the deposition of such highly active drugs like prostanoids.

[0058] The impact of SMI-TRE on ventilation-perfusion matching was assessed in five patients (30 µg TRE, n=2; 45 µg TRE, n=1; 60 µg TRE, n=2) with pre-existing gas exchange problems by use of the multiple inert gas elimination technique (MIGET), see e.g. Wagner P D, Saltzman H A, West J B. Measurement of continuous distributions of ventilation-perfusion ratios: theory. J Appl Physiol. 1974; 36:588-99; Ghofrani H A, Wiedemann R, Rose F, Schermuly R T, Olschewski H, Weissmann N et al. Sildenafil for treatment of

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lung fibrosis and pulmonary hypertension: a randomised controlled trial. *Lancet*. 2002;360:895-900, both incorporated herein in their entirety.

Statistics:

[0059] Mean values, standard deviation, standard error of the mean and 95% confidence intervals were calculated. Statistical analysis was done by use of a paired t-test.

Results:

[0060] The inhalation of treprostinil sodium from the metered dose inhaler (SMI-TRE) was well tolerated, only mild and transient cough for a maximum of one minute was reported. No systemic side effects like headache, flush, nausea or dizziness were observed.

[0061] Two to three breaths of SMI-TRE induced a strong pulmonary vasodilation that outlasted the observation time of 120 minutes (45 and 60 µg). The lower dose of 30 µg TRE induced a somewhat shorter effect on pulmonary vascular resistance; however, the maximal pulmonary vasodilation was comparable. In contrast, placebo inhalation did not induce pulmonary vasodilation. In fact a slight increase in PVR over the time of the right heart catheter investigation could be recorded following placebo inhalation (FIG. 1). The effect of SMI-TRE on systemic vascular resistance and pressure was very small and not clinically significant. Cardiac output was significantly increased over the whole observation period, whereas heart rate was rather unchanged. Gas exchange was not influenced by SMI-TRE (FIG. 2). The maximal changes in hemodynamic and gas-exchange parameters compared to baseline values are depicted in Table 2.

TABLE 2

Extremes of the relative changes of hemodynamic and gas exchange parameters compared to baseline after inhalation of Placebo (n = 4), 30 µg treprostinil (n = 12), 45 µg treprostinil (n = 9) and 60 µg treprostinil (n = 20). Highest (max) and lowest (min) values during the observation period are shown.				
	Placebo	30 µg TRE	45 µg TRE	60 µg TRE
PAP (min)	99.4 ± 3.0	83.4 ± 3.2	77.6 ± 6.8	79.5 ± 2.4
PVR (min)	101.4 ± 1.9	84.4 ± 4.4	71.4 ± 8.9	77.5 ± 3.7
CO (max)	99.7 ± 1.1	108.8 ± 3.8	108.6 ± 5.6	103.8 ± 2.0
SVR (min)	104.3 ± 4.3	97.7 ± 4.2	92 ± 3.9	91.3 ± 2.1
SAP (min)	102.7 ± 1.7	97.3 ± 1.9	96.1 ± 1.5	93.6 ± 2.9
HR (max)	105 ± 2.1	106.1 ± 2.9	99.1 ± 2.4	101.1 ± 0.9
SaO ₂ (min)	98.2 ± 0.4	101 ± 0.3	94.4 ± 1.8	95.8 ± 0.9
SvO ₂ (max)	104.5 ± 1.4	102.4 ± 1.3	104.5 ± 4.4	102 ± 1.0

Data are given as percent of baseline values (mean ± SEM).

PAP = pulmonary artery pressure;

PVR = pulmonary vascular resistance;

SVR = systemic vascular resistance;

CO = cardiac output;

SAP = systemic arterial pressure;

HR = heart rate;

SaO₂ = arterial oxygen saturation;

SvO₂ = central venous oxygen saturation.

[0062] The areas under the curve for PVR were calculated for placebo and the different SMI-TRE doses over the 120 minute observation period (FIG. 3). A dose effect of SMI-TRE with a trend to a more sustained effect with the two highest doses could be observed.

[0063] The inhalation of a highly concentrated aerosol can be in theory prone to disturbances of gas exchange because the deposition of even small amounts of aerosol may deliver

high doses locally and thereby antagonize the hypoxic pulmonary vasoconstriction in poorly ventilated areas. This would then lead to increased shunt flow or increase of low ventilation/perfusion (V/Q) areas. This question was addressed in five patients with the multiple inert gas elimination technique (MIGET), the gold-standard for intrapulmonary V/Q ratio determination. The MIGET patients were selected for pre-existing gas exchange limitations. Characteristics of these patients were: PAP 54.6±3.2 mmHg, PVR 892±88 dynes, SaO₂ 91.7±0.5%, SvO₂ 65.2±1.8%. Etiologies were iPAH (n=1), CTEPH (n=3), pulmonary fibrosis (n=1). The maximal relative reduction of SaO₂ after inhalation of SMI-TRE in these patients was -3.8±1.5% compared to baseline values. Shunt flow at baseline, NO-inhalation and 60 minutes after SMI-TRE was 6.4±4.3%, 5.4±3.0% and 8.3±3.4%, respectively (mean±95% confidence interval; FIG. 4).

[0064] No significant increase in low V/Q areas or shunt fraction after inhalation of SMI-TRE was observed, in fact the distribution of perfusion was not different to that at baseline and during nitric oxide inhalation. This proves an excellent intrapulmonary selectivity of SMI-TRE, which is also reflected by unchanged arterial oxygen saturation.

Conclusion:

[0065] Treprostinil is tolerated at high doses with no systemic side effects. The application of an effective amount of treprostinil in only few or even one single breath was achieved with a highly concentrated treprostinil sodium solution. Treprostinil can be applied by a metered dose inhaler, such as Respimat® soft mist inhaler.

EXAMPLE 2

Investigation of the Effects of Inhaled Treprostinil on Pulmonary Hemodynamics and Gas Exchanged in Severe Pulmonary Hypertension

[0066] This study investigated the effects of inhaled treprostinil on pulmonary vascular resistance in severe pulmonary hypertension and addressed systemic effects and gas exchange as well as tolerability and efficacy of high doses of treprostinil given in short time. A total of 123 patients with a mean pulmonary artery pressure of about 50 mmHg were investigated in three separate randomized studies. Inhaled treprostinil exerted potent sustained pulmonary vasodilation with excellent tolerability and could be safely applied in a few breaths or even one breath.

Summary:

[0067] Three different studies were conducted on a total of 123 patients by means of right heart catheterization: i) a randomized crossover-design study (44 patients), ii) a dose escalation study (31 patients) and iii) a study of reduction of inhalation time while keeping the dose fixed (48 patients). The primary endpoint was the change in pulmonary vascular resistance (PVR).

[0068] The mean pulmonary artery pressure of the enrolled patients was about 50 mmHg. Hemodynamics and patient characteristics were similar in all studies. In study i) TRE and Iloprost (ILO), at an inhaled dose of 7.5 µg, displayed comparable PVR decrease, with a significantly different time course (p<0.001), TRE exhibiting a more sustained effect on PVR (p<0.0001) and less systemic side effects. In study ii)

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placebo, 30 µg, 60 µg, 90 µg or 120 µg TRE were applied with drug effects being observed for 3 hours after inhalation. A near-maximal acute PVR decrease was observed at 30 µg TRE. In study iii) TRE was inhaled with a pulsed ultrasonic nebulizer, mimicking a metered dose inhaler. 15 µg TRE was inhaled with 18 pulses (TRE concentration 100 µg/ml), 9 pulses (200 µg/ml), 3 pulses (600 µg/ml), 2 pulses (1000 µg/ml) or 1 pulse (2000 µg/ml), each mode achieving comparable, sustained pulmonary vasodilation.

[0069] Inhaled treprostinil exerts sustained pulmonary vasodilation with excellent tolerability at doses, which may be inhaled in a few or even one breath. Inhaled treprostinil is advantageous to inhaled iloprost in terms of duration of effect and systemic side effects. Inhaled treprostinil is well tolerated in concentrations up to 2000 mg/ml (bringing down inhalation time to a single breath) and in high doses (up to 90 µg).

Methods:

[0070] All inhalations were performed with the Optineb® ultrasonic nebulizer (Nebutech, Elsenfeld, Germany).

[0071] Study i) was a randomized, open-label, single-blind crossover study. The primary objective was to compare the acute hemodynamic effects and the systemic side effects of inhaled treprostinil with inhaled iloprost at comparable doses. A total number of 44 patients with moderate to severe precapillary pulmonary hypertension were enrolled. Patient characteristics and hemodynamic as well as gas exchange parameters are outlined in Table 3.

effects were monitored for 60 minutes after each inhalation. Iloprost was inhaled at 4 µg/ml (6 min inhalation time; n=44) and treprostinil was inhaled at a concentration of 4 µg/ml (6 min inhalation; n=14), 8 µg/ml (6 min inhalation; n=14) or 16 µg/ml (3 min inhalation; n=16). Based on previous biophysical characterization of the ultrasonic device with iloprost- and treprostinil-solution, this corresponds to a total inhaled dose of 7.5 µg iloprost and treprostinil (4 µg/ml) and 15 µg treprostinil (8 µg/ml and 16 µg/ml), respectively.

[0073] Study ii) was a randomized, open-label, single blind, placebo controlled study. The primary objectives were to describe the pharmacodynamic and pharmacokinetic effects of inhaled treprostinil at a well tolerated dose (30 µg) and to explore the highest tolerated single dose. A total number of 31 patients inhaled either placebo or treprostinil; each patient received one inhalation. The first 16 patients were randomized to 30 µg TRE (16 µg/ml, n=8) or placebo (stock solution in a concentration corresponding to TRE 16 µg/ml). Subsequent patients received 60 µg TRE (32 µg/ml; n=6), 90 µg TRE (48 µg/ml; n=6) and 120 µg TRE (64 µg/ml; n=3). Inhalation time was 6 minutes in all groups. Hemodynamics and gas-exchange as well as arterial treprostinil concentrations were recorded for 180 minutes.

[0074] Study iii) was a randomized, open-label, single blind study. The primary objective was to explore the shortest possible inhalation time for a 15 µg dose of inhaled treprostinil. A total of 48 patients inhaled one dose of TRE during right heart catheter investigation. The drug was applied in 18,

TABLE 3

Patient characteristics, hemodynamic parameters and gas exchange values at baseline, before challenge with inhalative prostanoids.												
N	Age	Gender f/m	Etiology i/o/t/f	PAP [mmHg]	PVR [dyn * s * cm ⁻⁵]	SAP [mmHg]	CVP [mmHg]	PAWP [mmHg]	CO [l/min]	SaO2 [%]	SvO2 [%]	
1a	14	55.1 ± 4.8	11/3	4/4/2/4	53.8 ± 3.1	911 ± 102	95.4 ± 3.6	7.4 ± 1	8.0 ± 0.8	4.3 ± 0.4	93.8 ± 2	63.9 ± 2.4
1b	14	54.1 ± 3.3	10/4	1/6/5/2	47.4 ± 3.8	716 ± 80	90.6 ± 3.3	5.9 ± 1.4	6.4 ± 0.7	4.7 ± 0.4	92 ± 1	64.4 ± 2.3
1c	16	56 ± 2.9	7/9	6/3/6/1	47.5 ± 4.5	777 ± 102	92 ± 4.5	8.3 ± 1.4	8.6 ± 1.4	4.4 ± 0.5	91.4 ± 0.9	59.8 ± 2.6
2a	8	60.8 ± 4	4/4	2/2/3/1	51.9 ± 4.9	849 ± 152	95.9 ± 4.8	7.6 ± 1.4	11.1 ± 1.7	4.4 ± 0.6	89.6 ± 2.8	60.1 ± 2.8
2b	8	52.8 ± 6.6	6/2	1/3/3/1	49 ± 4	902 ± 189	92.4 ± 2.4	4.8 ± 1.1	7.2 ± 1.3	4.0 ± 0.4	92.4 ± 2.4	62.5 ± 1.7
2c	6	56.8 ± 5.9	4/2	0/2/2/2	44.2 ± 3.5	856 ± 123	96.3 ± 3.9	5 ± 1.1	6 ± 1	3.8 ± 0.3	92.8 ± 1.5	63.6 ± 1.8
2d	6	51.2 ± 3.8	4/2	2/2/2/0	55.5 ± 4.9	940 ± 110	91.2 ± 8.1	11.2 ± 1.2	10 ± 0.7	3.9 ± 0.4	92 ± 1.9	62 ± 5.8
2e	3	57.3 ± 9.1	1/2	0/1/0/2	45.3 ± 5.2	769 ± 267	99 ± 3.2	5 ± 2.1	9 ± 0.6	4.5 ± 0.6	94.2 ± 1.3	66.3 ± 1.5
3a	6	52.7 ± 6.6	4/2	2/4/0/0	53.8 ± 6.7	928 ± 145	92.7 ± 7.9	8.7 ± 2.7	8.8 ± 1.3	4.2 ± 0.6	90.4 ± 2.8	64.8 ± 4.3
3b	6	58.3 ± 3.5	4/2	3/1/1/1	54.2 ± 6.1	808 ± 156	94.3 ± 2.8	7 ± 1.4	10 ± 1.3	5 ± 0.7	91.9 ± 0.7	63.5 ± 2.9
3c	21	57.4 ± 5.6	8/3	7/7/6/1	46.1 ± 2.5	900 ± 99	88 ± 2.8	9 ± 1.4	9.2 ± 0.5	3.7 ± 0.3	91.7 ± 0.5	59.7 ± 2
3d	7	55.6 ± 5.8	3/4	0/4/3/0	53.1 ± 7.1	732 ± 123	91.4 ± 5.6	7.9 ± 3.1	8.6 ± 1.3	5 ± 0.4	90.7 ± 1.4	61.3 ± 3.7
3e	8	59 ± 5.2	7/1	0/4/4/0	45.1 ± 3.9	733 ± 114	92.8 ± 6.8	4.6 ± 0.8	8.1 ± 1.1	4.3 ± 0.2	90.7 ± 0.8	66.3 ± 2.8

Group 1 corresponds to study i); randomized crossover study comparing inhaled iloprost (ILO) and inhaled treprostinil (TRE). a = 7.5 g ILO vs. 7.5 µg TRE, b = 7.5 g ILO vs. 15 µg TRE (6 min inhalation time), c = 7.5 g ILO vs. 15 µg TRE (3 min inhalation time).

Group 2 corresponds to study ii); evaluation of maximal tolerated dose of TRE. a = placebo inhalation, b = 30 µg TRE, c = 60 µg TRE, d = 90 µg TRE, e = 120 µg TRE.

Group 3 corresponds to study iii); reduction of inhalation time by increase of TRE concentration, aiming at a total inhaled dose of 15 µg. a = 18 pulses of 100 µg/ml TRE, b = 9 pulses of 200 µg/ml TRE, c = 3 pulses of 600 µg/ml TRE, d = 2 pulses of 1000 µg/ml TRE, e = 1 pulse 2000 µg/ml TRE.

Etiology of pulmonary hypertension was classified as idiopathic PAH (i), PAH of other causes (o), chronic thromboembolic PH (t), and pulmonary fibrosis (f).

[0072] Each patient inhaled both iloprost and treprostinil on the same day during right heart catheter investigation; the drugs were administered consecutively with a one hour interval between the drug applications. One half of the study patients initially inhaled treprostinil and then inhaled iloprost (n=22), while the other half initially inhaled iloprost and then inhaled treprostinil (n=22). Patients were randomized to one of the two groups and blinded as to the study drugs. Drug

9, 3, 2 or 1 breaths. The aerosol was generated by a pulsed ultrasonic nebulizer (Ventaneb, Nebutech, Elsenfeld, Germany) in cycles consisting of 2 seconds aerosol production (pulse) and 4 seconds pause. The device included an opto-acoustical trigger for the patient to synchronize the inspiration to the end of the aerosol pulse, thereby providing exact dosage. The TRE dose of 15 µg was either generated during 18 cycles (Optineb filled with 100 µg/ml TRE, n=6), 9 cycles

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(200 µg/ml TRE, n=6), 3 cycles (600 µg/ml TRE, n=21), 2 cycles (1000 µg/ml TRE, n=7) or 1 cycle (2000 µg/ml TRE, n=8). Hemodynamics and gas exchange were recorded for 120-180 minutes.

[0075] Treprostinil plasma concentrations were assessed in study ii) at 10, 15, 30, 60 and 120 minutes after inhalation. Treprostinil quantification was done by Alta Analytical Laboratory (El Dorado Hills, Calif., USA) with a validated liquid chromatography atmospheric-pressure ionization tandem mass spectrometry as previously described Wade M., et al. J. Clin. Pharmacol. 2004;44:503-9. Mixed venous blood was drawn at the depicted time points (FIG. 11) after inhalation, centrifuged and the plasma frozen at -80° C. until temperature controlled shipping on dry ice.

Statistics:

[0076] For statistical analysis of study i) the repeated PVR measurements after inhaled iloprost and treprostinil were subjected to a three-factorial analysis of variance (ANOVA; factors: time (A), drug (B), treprostinil concentration (C)) to avoid multiple testing. The time to maximum PVR decrease after inhalation of iloprost versus treprostinil was compared by paired t-test. Area under the curve (AUC) was calculated from start of inhalation until 60 min after inhalation. Means, standard error of the mean (SEM) and 95% confidence intervals were calculated. For study ii) and iii) areas between curves (ABC) were calculated between placebo inhalation (study ii) and the respective treprostinil inhalation until 180 min (study ii)) and 120 min (study iii)) after end of inhalation.

Results:

[0077] The inhalation of iloprost as well as treprostinil in study i) resulted in a rapid decrease in PVR and PAP (FIG. 5-7). No significant differences were observed for the areas under the curve (AUC) of PVR decrease after inhalation of 7.5 µg TRE in 6 minutes (AUC -12.6±7.0%), 15 µg TRE in 6 minutes (AUC -13.3±3.2%) and 15 µg TRE in 3 minutes (AUC -13.6±4.3%). The AUC for PVR after the inhalation of 7.5 µg iloprost in 6 minutes was -7.7±3.7% (mean±95% confidence interval). An overview of the pooled data of treprostinil inhalation as compared to iloprost inhalation is given in FIG. 7. The maximum effect of iloprost and treprostinil on PVR was comparable but this effect was reached significantly later after treprostinil inhalation (18±2 min) compared to iloprost (8±1 min; mean±SEM, p<0.0001) and lasted considerably longer (after 60 min, PVR values in the treprostinil group had not yet returned to baseline). The increase in cardiac output was less acute but prolonged after treprostinil inhalation. Systemic arterial pressure (SAP) was unaffected by treprostinil inhalation, whereas a transient decrease was observed after iloprost inhalation. Iloprost and treprostinil did not affect gas exchange. Three-factorial ANOVA for PVR demonstrated a significant difference between repeated measurements after inhalation ($p_{(A)} < 0.0001$), no significant difference between drugs ($p_B = 0.1$), no difference between treprostinil concentrations ($p_{(C)} = 0.74$) and a significant drug×time interaction ($p_{(A \times B)} < 0.0001$). This translates into a significant effect of both drugs on PVR with comparable drug potency but a prolonged drug effect of treprostinil compared to iloprost.

[0078] In this study the occasionally observed mild side effects of iloprost inhalation at the given dose (transient flush, headache) were not observed with inhaled treprostinil. Bad

taste was reported by most of the patients after inhalation of TRE. This was later found to be attributable to the metacresol preservative contained in the treprostinil solution.

[0079] In study ii) pharmacodynamics of inhaled placebo or treprostinil were observed for 180 minutes. Placebo inhalation was followed by a gradual increase in PVR over the entire observation time. Due to reduced patient numbers in the 120 µg TRE group (because of side effects, see below), the hemodynamic values for this group were not included in the graphs of this study (FIG. 8-9). All TRE doses lead to comparable maximal decreases of PVR to 76.5±4.7% (30 µg), 73.7±5.8% (60 µg), 73.3±4.3% (90 µg) and 65.4±4.1% (120 µg) of baseline values. An extended duration of pulmonary vasodilation was noted, surpassing the 3 hour observation period for the 60 µg and 90 µg (and 120 µg) TRE doses, whereas in the 30 µg dose group the hemodynamic changes had just returned to baseline within this period. Even at the highest doses, TRE had only minor effects on systemic arterial pressure (FIG. 8). Cardiac output was increased to a maximum of 106.8±3.2% (30 µg), 122.9±4.3% (60 µg), 114.3±4.8% (90 µg) and 111.3±3.9% (120 µg TRE). The areas between the response curves after placebo versus TRE inhalation were calculated for PVR, PAP, SVR and SAP (FIG. 9). Areas between the curves for PVR were not significantly different for 30 µg, 60 µg and 90 µg TRE, a nearly maximal effect on PVR was already observed with 30 µg TRE. Effects on PAP and SAP were small and did not show a dose-response relationship. Gas exchange was not affected at doses up to 90 µg TRE, but arterial oxygen saturation was significantly decreased at a dose of 120 µg TRE in all 3 patients. Further dose increments were omitted due to this side effect and severe headache in one patient.

[0080] Again, bad taste of the TRE aerosol was reported by most patients. Other side effects were flushing (n=1; 30 µg TRE), mild transient cough (n=3; 60 µg TRE), mild transient bronchoconstriction that resolved after one inhalation of fenoterol (n=1; 30 µg TRE), moderate bronchoconstriction that resolved after one inhalation of fenoterol (n=1; 120 µg TRE), and severe headache (n=1; 120 µg TRE). The bad taste, the bronchoconstriction and the drop in SaO₂ was attributed to metacresol in the original TRE solution. With the use of a metacresol-free solution of TRE (University Hospital Gießen, Germany; produced according to the manufacturer's protocol) in the following study, these side effects did no longer occur.

[0081] Study iii) was performed with metacresol-free TRE solution, having no specific taste and smell. A total of 48 patients were enrolled. This study aimed at the reduction of inhalation time and aerosol volume needed for pulmonary drug delivery. A modified Optineb inhalation device was programmed to produce a constant amount of aerosol during repeatable pulses of aerosol generation. With this device, treprostinil could be safely utilized up to a concentration of 2000 µg/ml without considerable side effects. No relationship of number or type of side effects to TRE concentration was observed. Reported side effects were mild transient cough (n=6), mild headache (n=2) and mild jaw pain (n=1).

[0082] The reduction of PVR and PAP was comparable between all groups (FIG. 10). TRE inhalation reduced PVR to 76.3±5.6% (18 pulses, 100 µg/ml), 72.9±4.9% (9 pulses, 200 µg/ml), 71.2±6.0% (3 pulses, 600 µg/ml), 77.4±4.5% (2 pulses, 1000 µg/ml) and 80.3±5.2% (1 pulse, 2000 µg/ml). PAP was reduced to 84.2±4.5% (18 pulses, 100 µg/ml), 84.2±4.1% (9 pulses, 200 µg/ml), 81.1±4.1% (3 pulses, 600

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$\mu\text{g/ml}$), $86 \pm 4\%$ (2 pulses, $1000 \mu\text{g/ml}$) and $88 \pm 5.4\%$ (1 pulse, $2000 \mu\text{g/ml}$). Cardiac output was moderately increased in all groups, whereas systemic arterial pressure was not significantly affected.

[0083] The areas between the curves (ABC) for changes in hemodynamic and gas-exchange parameters after inhalation of $15 \mu\text{g}$ TRE versus placebo were calculated for an observation time of 120 minutes (FIG. 11). The ABC for both PVR and PAP was comparable between all groups.

[0084] Pharmacokinetic results from study ii): Peak plasma concentrations of treprostinil were found 10-15 minutes after inhalation. Maximal treprostinil plasma concentrations (C_{max}) for the $30 \mu\text{g}$, $60 \mu\text{g}$, $90 \mu\text{g}$ and $120 \mu\text{g}$ doses were $0.65 \pm 0.28 \text{ ng/ml}$ ($n=4$), $1.59 \pm 0.17 \text{ ng/ml}$ ($n=4$), 1.74 ng/ml ($n=1$) and $3.51 \pm 1.04 \text{ ng/ml}$ ($n=2$), respectively (mean \pm SEM; FIG. 12).

Discussion:

[0085] These studies investigated whether i) the acute effects of inhaled treprostinil would be comparable to or possibly advantageous over inhaled iloprost in pulmonary hypertensive patients, ii) the inhaled prostanoid dose might be increased without substantial local or systemic side effects, and iii) if the time of inhalation, which is 6-12 minutes for iloprost, could be reduced significantly by increasing the concentration of treprostinil aerosol.

[0086] The patient population in these studies included different forms of precapillary pulmonary hypertension. All these patients had a need for therapy of pulmonary hypertension and reflected the typical population of a pulmonary hypertension center. No major differences in patient characteristics or hemodynamic baseline values existed between the different groups (table 3).

[0087] In study i) it was shown that the inhalation of treprostinil and iloprost in similar doses resulted in a comparable maximum pulmonary vasodilatory effect. However, marked differences in the response profile were noted. The onset of the pulmonary vasodilatory effect of inhaled treprostinil was delayed compared to iloprost, but lasted considerably longer, with the PVR decrease continuing beyond the one-hour observation period. Although the average dose of treprostinil was higher than the iloprost dose, no systemic effects were noted after treprostinil inhalation, whereas flush and transient SAP decrease, accompanied by more prominent cardiac output increase, occurred after iloprost inhalation. Such side effects were more prominent than in previous studies with inhaled iloprost. This may have been caused by the fact that the iloprost dose used in this study was 50% higher than the recommended single inhalation dose ($5 \mu\text{g}$) and that the preceding treprostinil inhalation may have added to the systemic side effects caused by the iloprost inhalation. Surprisingly, with TRE there was no such systemic side effect, although the average effect on PVR was as potent as with iloprost.

[0088] This study used a cross-over design in order to minimize the effects of inter-individual differences in response to prostanoids. The short observation period of 1 hour was used to avoid an uncomfortably long catheter investigation. As a study limitation, the short observation interval may have caused carryover effects of the first to the second period as suggested by FIG. 5. However, this still allowed for the interpretation of the study, that both drugs are potent pulmonary vasodilators and that treprostinil effects are significantly sustained compared to the iloprost effects.

[0089] The longer duration of action and the virtual absence of side effects (except the bitter taste of treprostinil aerosol, later attributed to metacresol) encouraged increasing the applied treprostinil dose in study ii). Observation time was extended to 3 hours to obtain precise pharmacodynamic data. Inhaled treprostinil resulted in a strong pulmonary vasodilation that outlasted the observation time of 3 hours when compared to placebo inhalation. Surprisingly, inhaled treprostinil was tolerated in doses up to $90 \mu\text{g}$.

[0090] Study iii) successfully demonstrated that the inhalation time could be reduced to literally one single breath of $2000 \mu\text{g/ml}$ treprostinil solution, thereby applying a dose of $15 \mu\text{g}$. This drug administration with a single breath induced pulmonary vasodilation for longer than 3 hours compared to placebo inhalation. Side effects were minor, of low frequency and not related to drug concentration. It was a surprising finding that such high concentrations of treprostinil were so well tolerated.

Conclusion:

[0091] Inhaled treprostinil can be applied in high doses (up to $90 \mu\text{g}$) with a minimal inhalation time. Inhaled treprostinil exerts high pulmonary selectivity and leads to a long-lasting pulmonary vasodilation.

[0092] Although the foregoing refers to particular preferred embodiments, it will be understood that the present invention is not so limited. It will occur to those of ordinary skill in the art that various modifications may be made to the disclosed embodiments and that such modifications are intended to be within the scope of the present invention.

[0093] All of the publications, patent applications and patents cited in this specification are incorporated herein by reference in their entirety.

What is claimed is:

1. A method for treating pulmonary hypertension, comprising administering to a subject in need thereof treprostinil or treprostinil derivative, or a pharmaceutically acceptable salt thereof by a metered dose inhaler.
2. The method of claim 1, wherein said metered dose inhaler is a pressured metered dose inhaler.
3. The method of claim 1, wherein said metered dose inhaler is a dry powder inhaler.
4. The method of claim 1, wherein said metered dose inhaler is a soft mist inhaler.
5. The method of claim 4, wherein said treprostinil is formulated in said inhaler as a solution, wherein a solvent of the solution comprises water, ethanol or a mixture thereof.
6. The method of claim 5, wherein a concentration of the treprostinil in the solution ranges from about $500 \mu\text{g/ml}$ to about $2500 \mu\text{g/ml}$.
7. The method of claim 6, wherein the concentration of the treprostinil in the solution ranges from about $1000 \mu\text{g/ml}$ to about $2000 \mu\text{g/ml}$.
8. The method of claim 1, wherein a dose of the treprostinil administered during a single event ranges from about $15 \mu\text{g}$ to about $100 \mu\text{g}$ of the treprostinil.
9. The method of claim 8, wherein the dose ranges from about $30 \mu\text{g}$ to about $90 \mu\text{g}$ of the treprostinil.
10. The method of claim 1, wherein said administering does not have a systemic side effect on said subject, wherein the systemic side effect is selected from the group consisting of headache, flush, nausea, and dizziness.
11. The method of claim 1, wherein said administering does not disrupt gas exchange in said subject.

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12. The method of claim 1, wherein said administering does change heart rate of said subject.

13. The method of claim 1, wherein said administering does not affect systemic arterial pressure and systemic arterial resistance.

14. The method of claim 1, wherein said administering comprises a limited number of breaths by said subject.

15. The method of claim 1, wherein said administering lasts less than 5 minutes.

16. The method of claim 1, wherein said administering lasts less than 1 minute.

17. The method of claim 1, wherein said subject is a human being.

18. The method of claim 1, further comprising administering to said subject at least one supplementary agent selected from the group consisting of diltiazem, amlodipine, nifedipine, sildenafil, tadalafil, vardenafil, bosentan, sitaxsentan, ambrisentan, prostacyclin, iloprost, beraprost and pharmaceutically acceptable salts thereof.

19. A method of delivering to a subject in need thereof a therapeutically effective amount of treprostinil, or treprostinil derivative or a pharmaceutically acceptable salt thereof comprising administering to the subject the therapeutically effective amount of the treprostinil or treprostinil derivative or a pharmaceutically acceptable salt thereof using a metered dose inhaler.

20. The method of claim 19, wherein said metered dose inhaler is a pressurized metered dose inhaler.

21. The method of claim 19, wherein said metered dose inhaler is a dry powder inhaler.

22. The method of claim 19, wherein said metered dose inhaler is a soft mist inhaler.

23. The method of claim 22, wherein said treprostinil is formulated in the metered dose inhaler as a solution, wherein a solvent of the solution comprises water, ethanol or a mixture thereof.

24. The method of claim 23, wherein a concentration of the treprostinil in the solution ranges from about 500 µg/ml to about 2500 µg/ml.

25. The method of claim 24, wherein the concentration of the treprostinil in the solution ranges from about 1000 µg/ml to about 2000 µg/ml.

26. The method of claim 19, wherein a dose of the treprostinil administered during a single event ranges from about 15 µg to about 100 µg of the treprostinil.

27. The method of claim 26, wherein the dose ranges from about 30 µg to about 90 µg of the treprostinil.

28. The method of claim 19, wherein said administering does not have a systemic side effect on said subject, wherein the systemic side effect is selected from the group consisting of headache, flush, nausea, and dizziness.

29. The method of claim 19, wherein said administering does not disrupt gas exchange in said subject.

30. The method of claim 19, wherein said administering does change heart rate of said subject.

31. The method of claim 19, wherein said administering does not affect systemic arterial pressure and systemic arterial resistance.

32. The method of claim 19, wherein said administering comprises a limited number of breaths by said subject.

33. The method of claim 19, wherein said administering lasts less than 5 minutes.

34. The method of claim 19, wherein said administering lasts less than 1 minute.

35. The method of claim 19, wherein said subject is a human being.

36. A kit for treating pulmonary hypertension, comprising (i) a metered dose inhaler containing a pharmaceutical formulation comprising treprostinil or treprostinil derivative, or a pharmaceutically acceptable salt thereof, and (ii) instructions for use of in treating pulmonary hypertension.

37. The kit of claim 36, wherein said metered dose inhaler is a pressurized metered dose inhaler.

38. The kit of claim 36, wherein said metered dose inhaler is a dry powder inhaler.

39. The kit of claim 36, wherein said metered dose inhaler is a soft mist inhaler.

40. The kit of claim 39, wherein said formulation further comprises water, ethanol or a mixture thereof.

41. The kit of claim 36, wherein a concentration of the treprostinil in said formulation is from about 500 µg/ml to about 2500 µg/ml.

42. The kit of claim 41, wherein said concentration is from about 1000 µg/ml to about 2000 µg/ml.

43. The kit of claim 36, further comprising an effective amount of at least one supplementary agent selected from the group consisting of diltiazem, amlodipine, nifedipine, sildenafil, tadalafil, vardenafil, bosentan, sitaxsentan, ambrisentan, prostacyclin, iloprost, beraprost and pharmaceutically acceptable salts thereof.

44. A kit comprising a metered dose inhaler containing a pharmaceutical formulation comprising treprostinil or treprostinil derivative, or a pharmaceutically acceptable salt thereof.

45. The kit of claim 44, wherein said metered dose inhaler is a pressurized metered dose inhaler.

46. The kit of claim 44, wherein said metered dose inhaler is a dry powder inhaler.

47. The kit of claim 44, wherein said metered dose inhaler is a soft mist inhaler.

48. The kit of claim 47, wherein said formulation further comprises water, ethanol or a mixture thereof.

49. The kit of claim 44, wherein a concentration of the treprostinil in said formulation is from about 500 µg/ml to about 2500 µg/ml.

50. The kit of claim 44, wherein said concentration is from about 1000 µg/ml to about 2000 µg/ml.

51. The kit of claim 44, further comprising instructions for using the metered dose inhaler for inhaling the treprostinil.

* * * * *

EXHIBIT 13

(12) **United States Patent**
Olschewski et al.

(10) **Patent No.:** **US 9,358,240 B2**
(45) **Date of Patent:** **Jun. 7, 2016**

(54) **TREPROSTINIL ADMINISTRATION BY INHALATION**

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(58) **Field of Classification Search**
CPC .. A61K 31/5575; A61K 31/557; A61K 9/008
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See application file for complete search history.

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(57) **ABSTRACT**

Treprostinil can be administered using a metered dose inhaler. Such administration provides a greater degree of autonomy to patients. Also disclosed are kits that include a metered dose inhaler containing a pharmaceutical formulation containing treprostinil.

9 Claims, 12 Drawing Sheets

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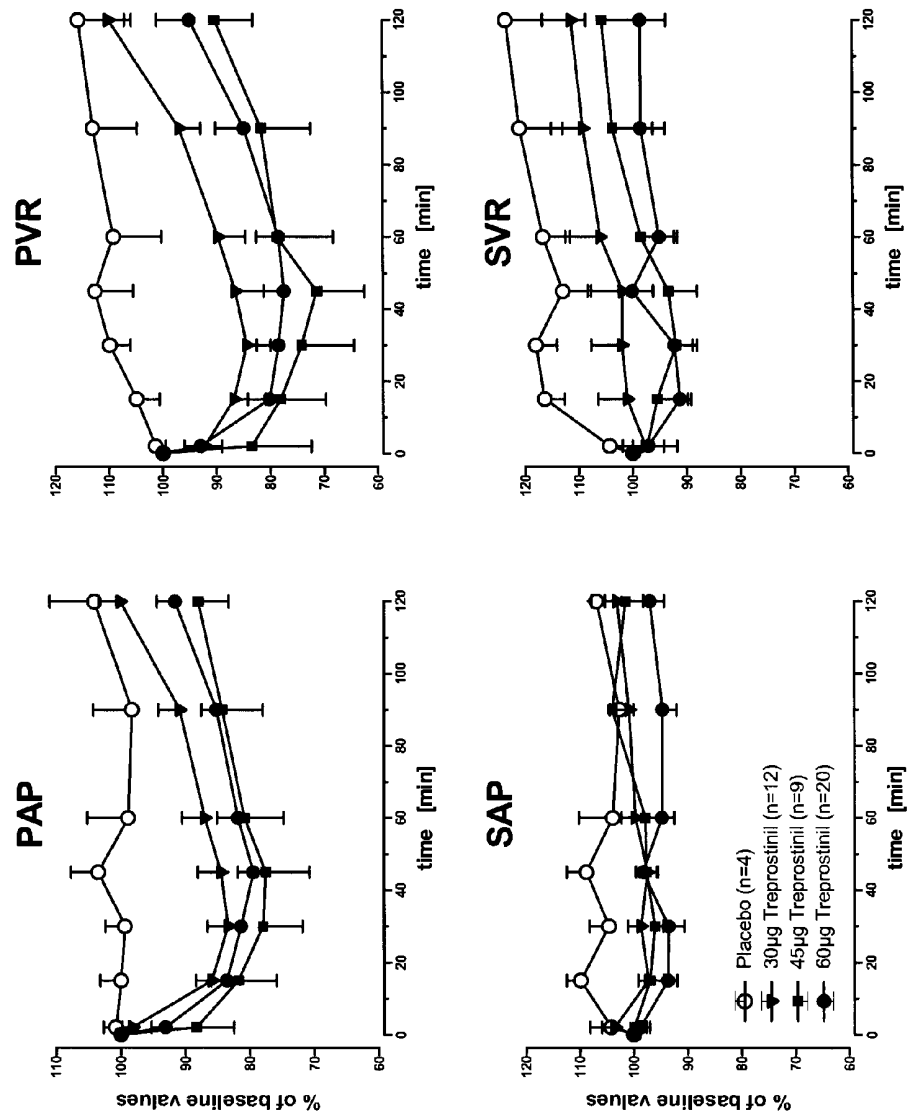
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FIGURE 1



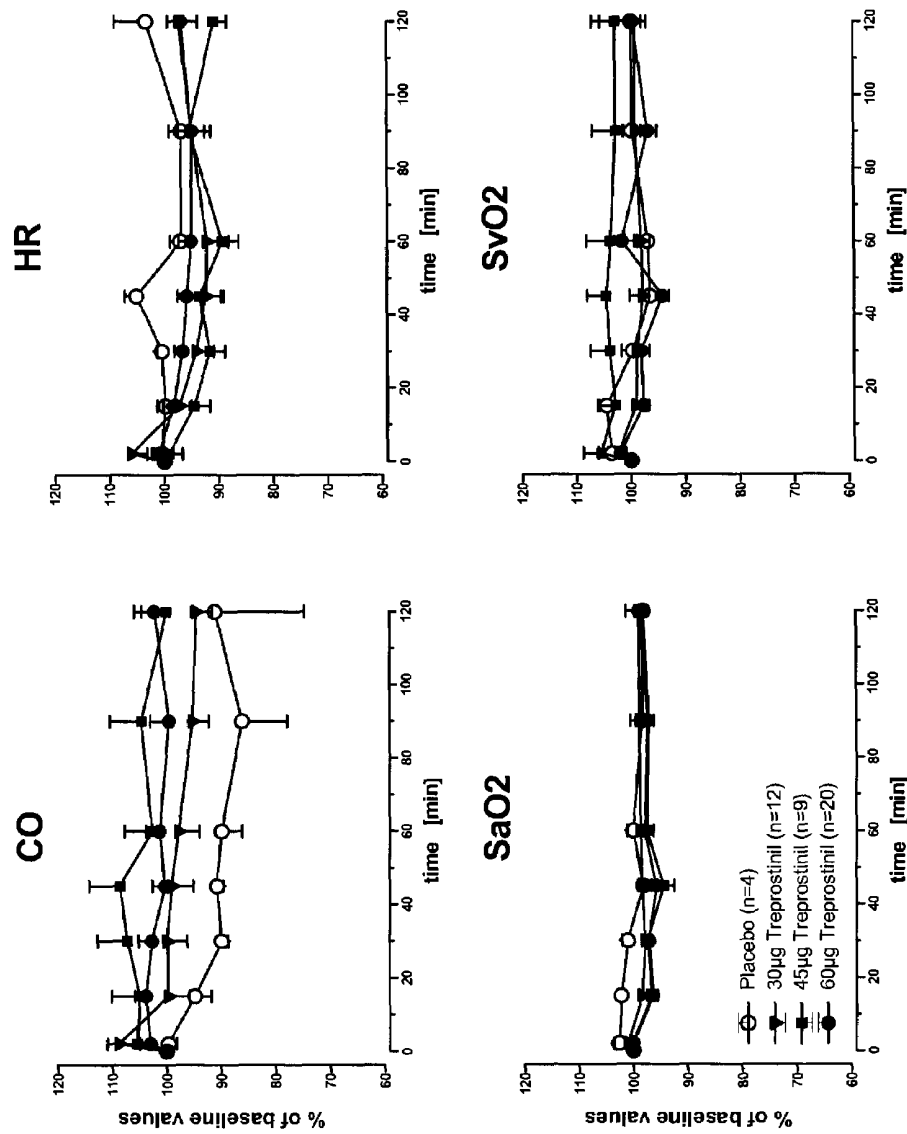
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FIGURE 2



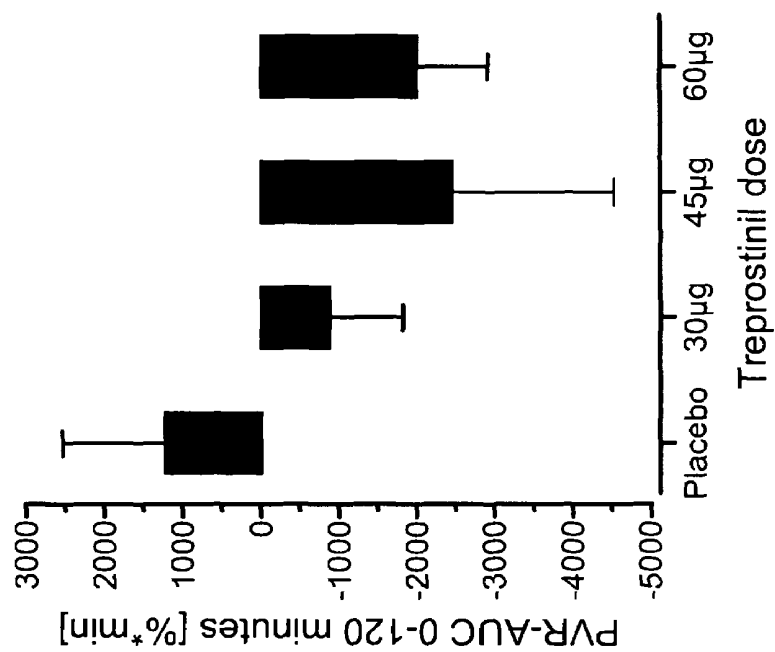
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FIGURE 3



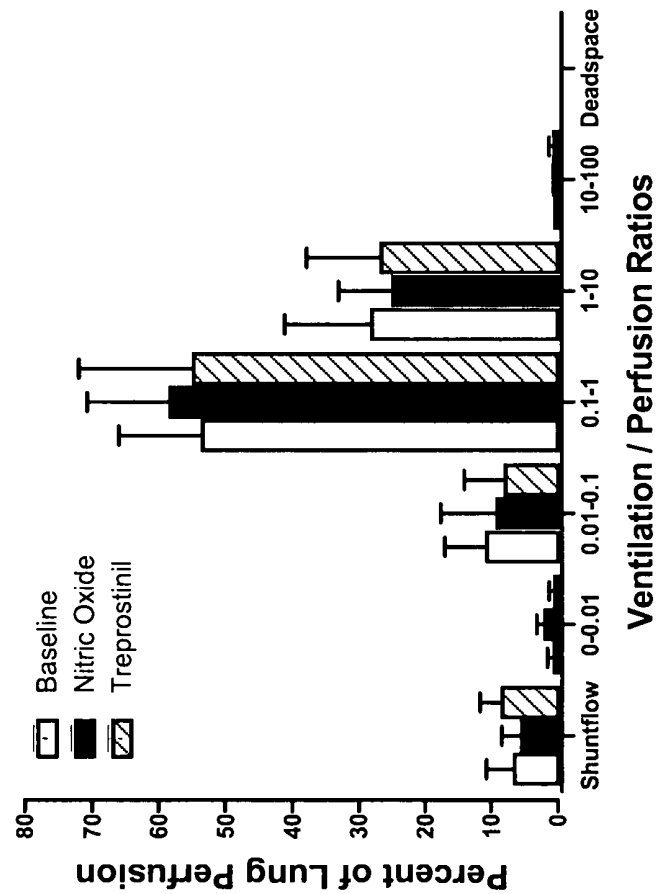
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FIGURE 4



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FIGURE 5

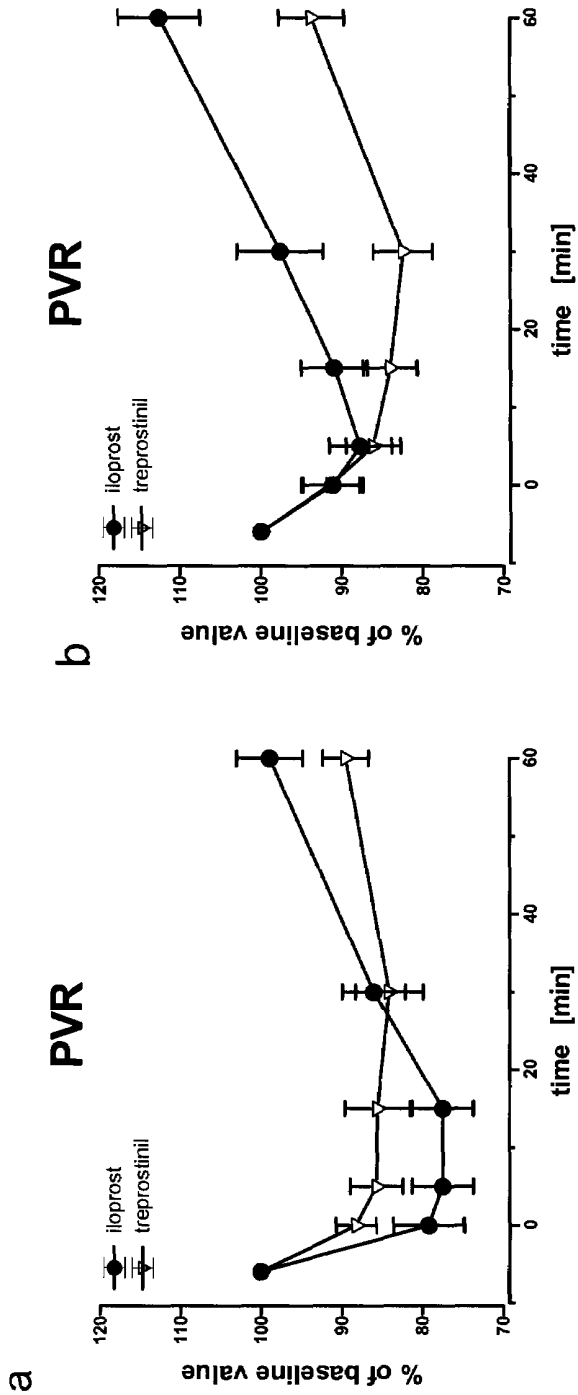
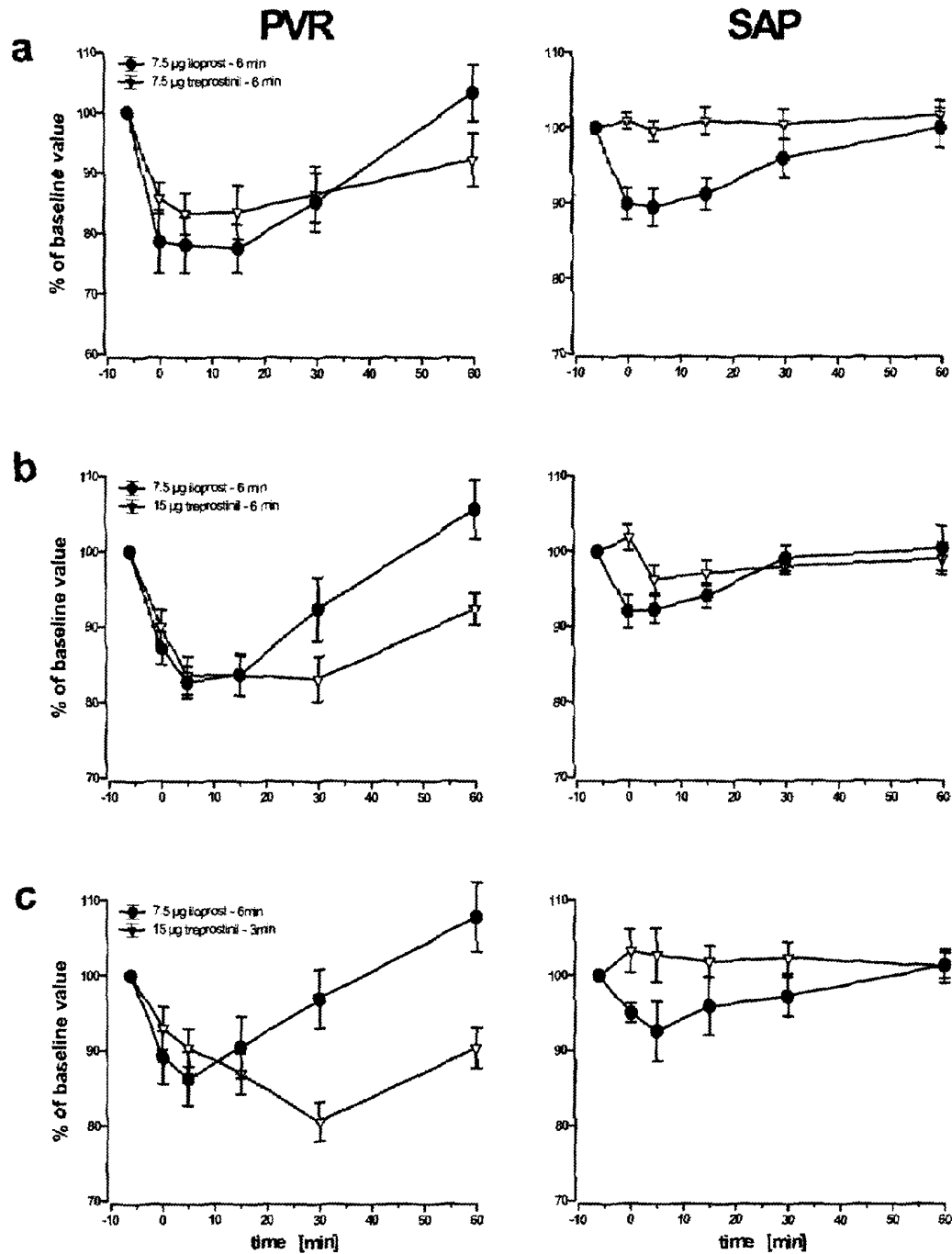


FIGURE 6



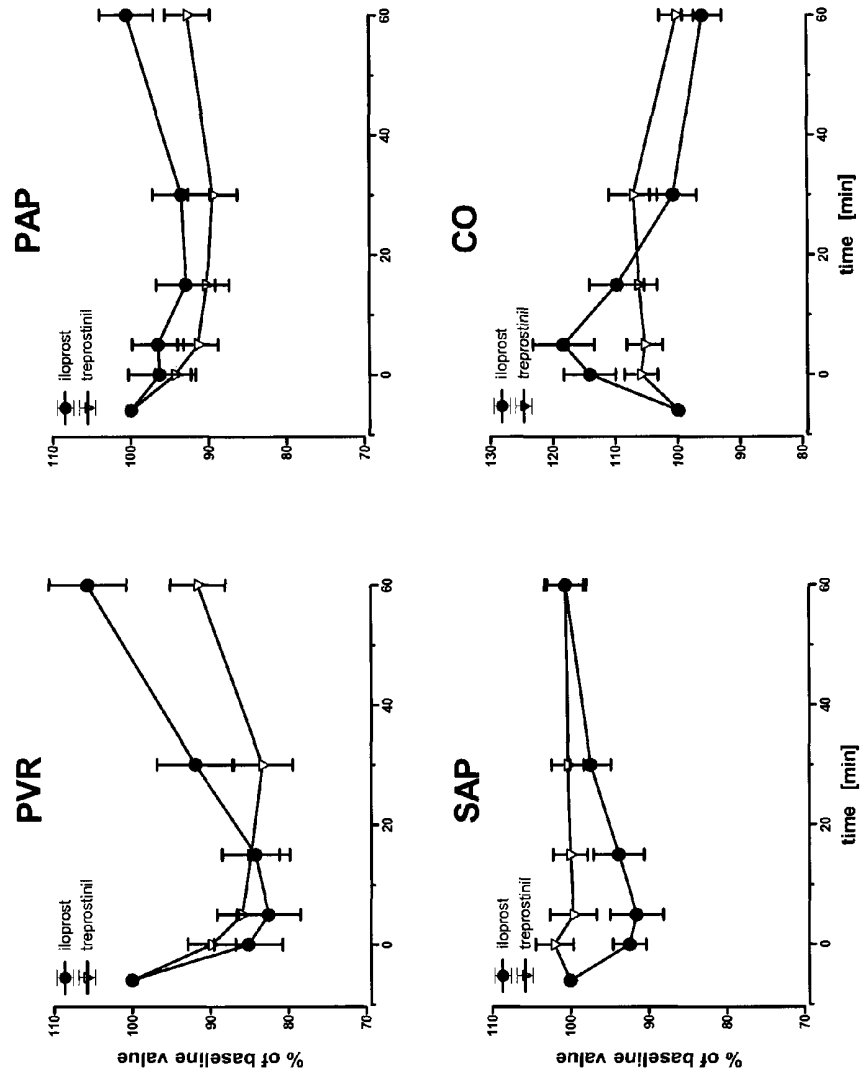
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FIGURE 7



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FIGURE 8

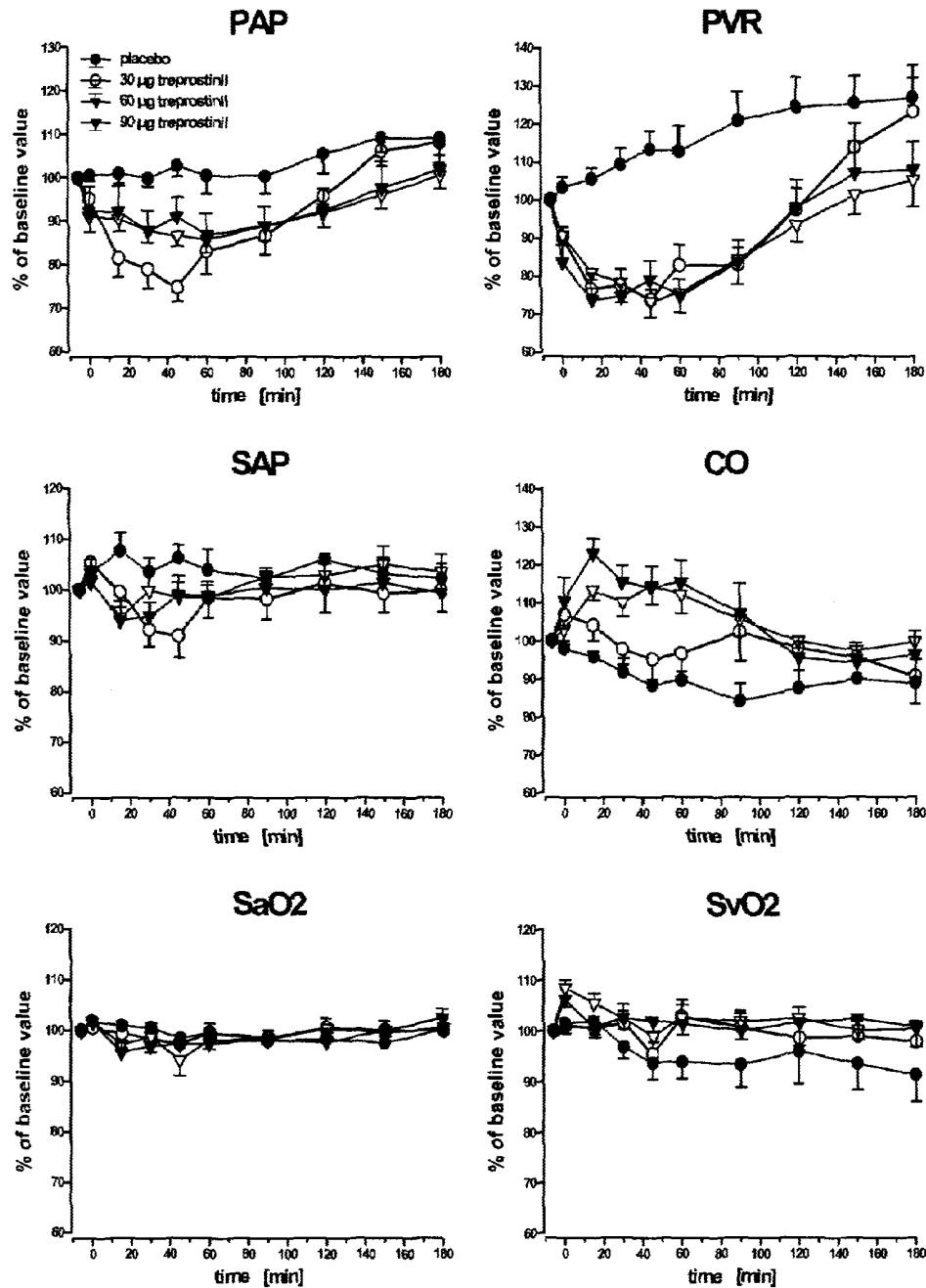
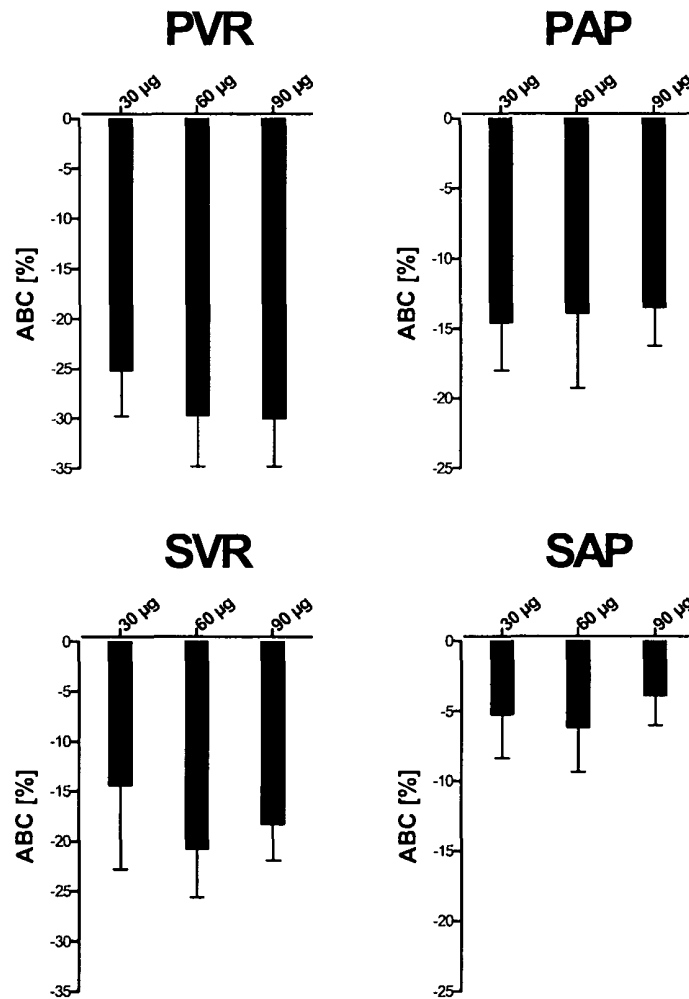


FIGURE 9



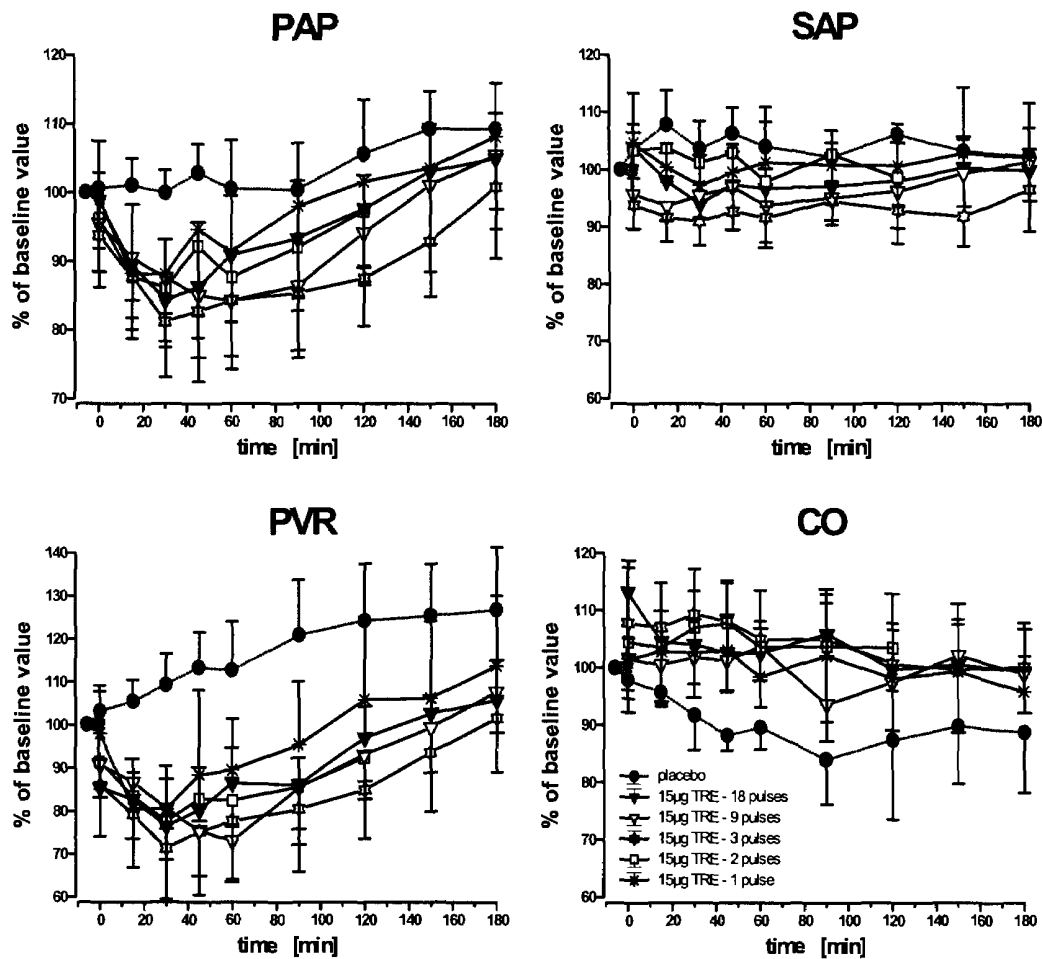
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FIGURE 10



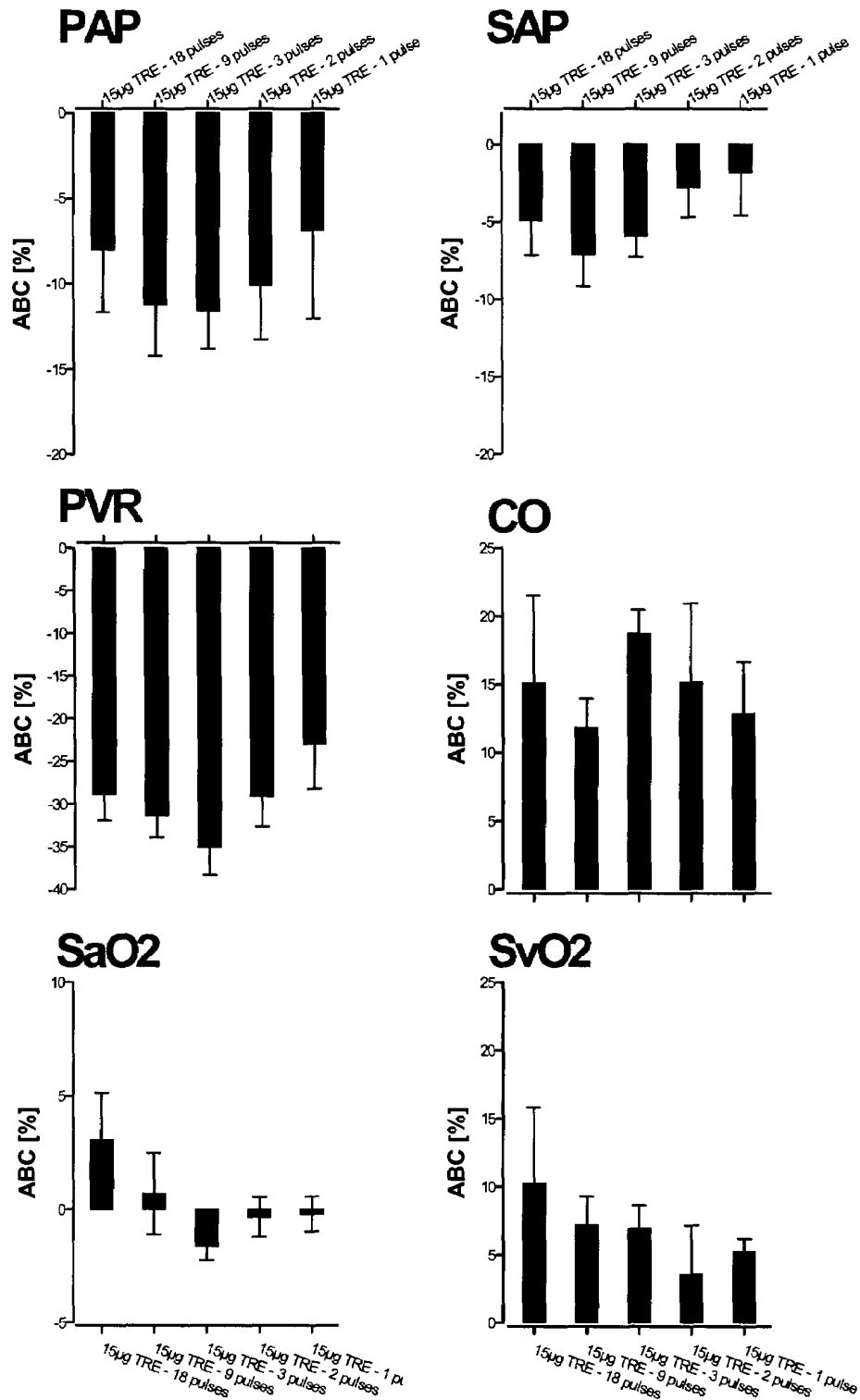
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FIGURE 11



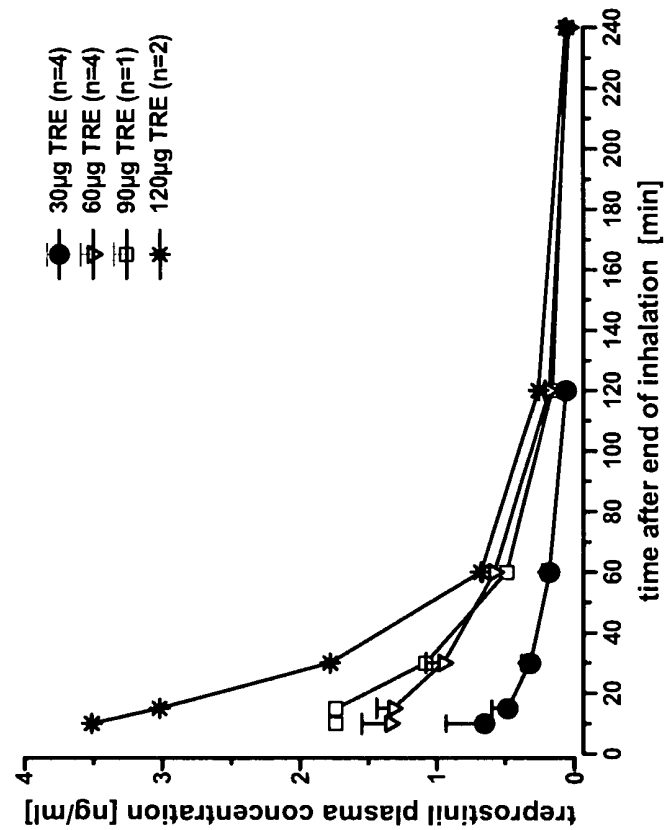
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FIGURE 12



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TREPROSTINIL ADMINISTRATION BY INHALATION

CROSS REFERENCE TO RELATED APPLICATIONS

The present application is a Continuation of U.S. application Ser. No. 11/748,205, filed May 14, 2007, which claims priority to U.S. provisional application No. 60/800,016 filed May 15, 2006, which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

The present application relates to methods and kits for therapeutic treatment and, more particularly, to therapeutic methods involving administering treprostinil using a metered dose inhaler and related kits.

BACKGROUND OF THE INVENTION

All blood is driven through the lungs via the pulmonary circulation in order, among other things, to replenish the oxygen which it dispenses in its passage around the rest of the body via the systemic circulation. The flow through both circulations is in normal circumstances equal, but the resistance offered to it in the pulmonary circulation is generally much less than that of the systemic circulation. When the resistance to pulmonary blood flow increases, the pressure in the circulation is greater for any particular flow. The above described condition is referred to as pulmonary hypertension (PH). Generally, pulmonary hypertension is defined through observations of pressures above the normal range pertaining in the majority of people residing at the same altitude and engaged in similar activities.

Pulmonary hypertension may occur due to various reasons and the different entities of pulmonary hypertension were classified based on clinical and pathological grounds in 5 categories according to the latest WHO convention, see e.g. Simonneau G., et al. J. Am. Coll. Cardiol. 2004; 43(12 Suppl S):5S-12S. Pulmonary hypertension can be a manifestation of an obvious or explicable increase in resistance, such as obstruction to blood flow by pulmonary emboli, malfunction of the heart's valves or muscle in handling blood after its passage through the lungs, diminution in pulmonary vessel caliber as a reflex response to alveolar hypoxia due to lung diseases or high altitude, or a mismatch of vascular capacity and essential blood flow, such as shunting of blood in congenital abnormalities or surgical removal of lung tissue. In addition, certain infectious diseases, such as HIV and liver diseases with portal hypertension may cause pulmonary hypertension. Autoimmune disorders, such as collagen vascular diseases, also often lead to pulmonary vascular narrowing and contribute to a significant number of pulmonary hypertension patients. The cases of pulmonary hypertension remain where the cause of the increased resistance is as yet inexplicable are defined as idiopathic (primary) pulmonary hypertension (iPAH) and are diagnosed by and after exclusion of the causes of secondary pulmonary hypertension and are in the majority of cases related to a genetic mutation in the bone morphogenetic protein receptor-2 gene. The cases of idiopathic pulmonary arterial hypertension tend to comprise a recognizable entity of about 40% of patients cared for in large specialized pulmonary hypertension centers. Approximately 65% of the most commonly afflicted are female and young adults, though it has occurred in children and patients over 50. Life expectancy from the time of diagnosis is short without

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specific treatment, about 3 to 5 years, though occasional reports of spontaneous remission and longer survival are to be expected given the nature of the diagnostic process. Generally, however, disease progress is inexorable via syncope and right heart failure and death is quite often sudden.

Pulmonary hypertension refers to a condition associated with an elevation of pulmonary arterial pressure (PAP) over normal levels. In humans, a typical mean PAP is approximately 12-15 mm Hg. Pulmonary hypertension, on the other hand, can be defined as mean PAP above 25 mmHg, assessed by right heart catheter measurement. Pulmonary arterial pressure may reach systemic pressure levels or even exceed these in severe forms of pulmonary hypertension. When the PAP markedly increases due to pulmonary venous congestion, i.e. in left heart failure or valve dysfunction, plasma can escape from the capillaries into the lung interstitium and alveoli. Fluid buildup in the lung (pulmonary edema) can result, with an associated decrease in lung function that can in some cases be fatal. Pulmonary edema, however, is not a feature of even severe pulmonary hypertension due to pulmonary vascular changes in all other entities of this disease.

Pulmonary hypertension may either be acute or chronic. Acute pulmonary hypertension is often a potentially reversible phenomenon generally attributable to constriction of the smooth muscle of the pulmonary blood vessels, which may be triggered by such conditions as hypoxia (as in high-altitude sickness), acidosis, inflammation, or pulmonary embolism. Chronic pulmonary hypertension is characterized by major structural changes in the pulmonary vasculature, which result in a decreased cross-sectional area of the pulmonary blood vessels. This may be caused by, for example, chronic hypoxia, thromboembolism, collagen vascular diseases, pulmonary hypercirculation due to left-to-right shunt, HIV infection, portal hypertension or a combination of genetic mutation and unknown causes as in idiopathic pulmonary arterial hypertension.

Pulmonary hypertension has been implicated in several life-threatening clinical conditions, such as adult respiratory distress syndrome ("ARDS") and persistent pulmonary hypertension of the newborn ("PPHN"). Zapol et al., Acute Respiratory Failure, p. 241-273, Marcel Dekker, New York (1985); Peckham, J. Ped. 93:1005 (1978). PPHN, a disorder that primarily affects full-term infants, is characterized by elevated pulmonary vascular resistance, pulmonary arterial hypertension, and right-to-left shunting of blood through the patent ductus arteriosus and foramen ovale of the newborn's heart. Mortality rates range from 12-50%. Fox, Pediatrics 59:205 (1977); Dworetz, Pediatrics 84:1 (1989). Pulmonary hypertension may also ultimately result in a potentially fatal heart condition known as "cor pulmonale," or pulmonary heart disease. Fishman, "Pulmonary Diseases and Disorders" 2nd Ed., McGraw-Hill, New York (1988).

Currently, there is no treatment for pulmonary hypertension that can be administered using a compact inhalation device, such as a metered dose inhaler.

SUMMARY OF THE INVENTION

One embodiment is a method of delivering to a subject in need thereof a therapeutically effective amount of treprostinil, or treprostinil derivative or a pharmaceutically acceptable salt thereof comprising administering to the subject a therapeutically effective amount of the treprostinil or treprostinil derivative or a pharmaceutically acceptable salt thereof using a metered dose inhaler.

Another embodiment is a method for treating pulmonary hypertension comprising administering to a subject in need

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thereof treprostinil or its derivative, or a pharmaceutically acceptable salt thereof using a metered dose inhaler.

Yet another embodiment is a kit comprising a metered dose inhaler containing a pharmaceutical formulation comprising treprostinil or treprostinil derivative, or a pharmaceutically acceptable salt thereof.

And yet another embodiment is a kit for treating pulmonary hypertension in a subject, comprising (i) an effective amount of treprostinil or its derivative, or a pharmaceutically acceptable salt thereof; (ii) a metered dose inhaler; (iii) instructions for use in treating pulmonary hypertension.

Administration of treprostinil using a metered dose inhaler can provide patients, such as pulmonary hypertension patients, with a high degree of autonomy.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 pulmonary and systemic changes in hemodynamics following the inhalation of placebo (open circles), 30 µg treprostinil (triangles), 45 µg treprostinil (squares) or 60 µg TREprostinil (black circles) applied by a Metered Dose Inhaler (MDI-TRE). A single short inhalation of treprostinil induced sustained reduction of PAP and PVR that outlasted the observation period of 120 minutes at doses of 45 and 60 µg MDI-TRE. Systemic arterial pressure and resistance were not significantly affected. PAP=mean pulmonary artery pressure; PVR=pulmonary vascular resistance; SAP=mean systemic arterial pressure; SVR=systemic vascular resistance. Data are given as mean value±standard error of the mean (SEM).

FIG. 2 presents hemodynamic changes induced by the inhalation of placebo (open circles), 30 µg treprostinil (triangles), 45 µg treprostinil (squares) or 60 µg treprostinil (black circles) applied by a metered dose inhaler. Treprostinil induced sustained elevation of cardiac output. Heart rate was rather unchanged as a sign for low spillover of MDI-TRE to the systemic circulation. Gas exchange was not negatively affected. CO=cardiac output; HR=heart rate; SaO₂=arterial oxygen saturation; SvO₂=central venous oxygen saturation. Data are given as mean value±SEM.

FIG. 3 shows areas under the curve for changes in pulmonary vascular resistance (PVR) calculated for an observation period of 120 minutes after inhalation treprostinil using a metered dose inhaler. PVR was markedly lowered by treprostinil inhalation. The increased pulmonary vasodilation over time with the two highest doses mainly relies on the more sustained effect over time. Data are shown as mean value±95% confidence intervals.

FIG. 4 demonstrates Ventilation-perfusion matching measured with the multiple inert gas elimination technique. Five patients (30 µg TRE, n=2; 45 µg TRE, n=1; 60 µg TRE, n=2) with pre-existing gas exchange problems were investigated for changes in ventilation-perfusion ratios. All patients had significant shunt flow at baseline. Shunt-flow and low V/Q areas were not significantly changed by nitric oxide (NO) inhalation or treprostinil inhalation using a metered dose inhaler (MDI-TRE). MDI-TRE applied at high treprostinil concentrations did not negatively affect ventilation-perfusion matching and gas-exchange. Data are given as mean value±95% confidence intervals.

FIG. 5 presents response of pulmonary vascular resistance (PVR) to inhaled treprostinil vs. iloprost—period effects. a) First inhalation with treprostinil (n=22) vs. first inhalation with iloprost (n=22); b) second inhalation with treprostinil (n=22) vs. second inhalation with iloprost (n=22). The PVR decrease with treprostinil was delayed and prolonged, com-

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pared to iloprost. Due to carryover effects from the first period, in the second period, the effects of both drugs appeared shortened. Data are shown as percent of baseline values (mean value±95% confidence interval).

FIG. 6 presents response of PVR and systemic arterial pressure (SAP) to inhalation of treprostinil vs. iloprost—dose effects. a) Inhalation of 7.5 µg iloprost (in 6 min) vs. 7.5 µg treprostinil (6 min) (n=14, in a randomized order). b) Inhalation of 7.5 µg iloprost (6 min) vs. 15 µg treprostinil (6 min) (n=14, in randomized order). c) Inhalation of 7.5 µg iloprost (6 min) vs. 15 µg treprostinil (3 min) (n=16, in randomized order). Data are shown as percent of baseline values (mean±95% confidence interval). Iloprost, filled circles; Treprostinil, open triangles.

FIG. 7 presents hemodynamic response to inhalation of treprostinil vs. iloprost. Data from n=44 patients, who inhaled both drugs in randomized order, shown as percent of baseline values (mean value±95% confidence interval). PVR, pulmonary vascular resistance; PAP, mean pulmonary arterial pressure; SAP, mean systemic arterial pressure; CO, cardiac output.

FIG. 8 presents pharmacodynamics after treprostinil inhalation vs. placebo. Placebo or treprostinil in doses of 30 µg, 60 µg or 90 µg were inhaled (means±95% confidence intervals). Maximal decrease of PVR was comparable for all doses. The duration of pulmonary vasodilation (PVR-decrease) appeared to be dose dependent. PVR, pulmonary vascular resistance; PAP, mean pulmonary arterial pressure; SAP, mean systemic arterial pressure; CO, cardiac output; SaO₂, arterial oxygen saturation; SvO₂, mixed venous oxygen saturation.

FIG. 9 presents Areas Between the placebo and the treprostinil Curves (ABC). ABCs were calculated for a 3-hour period after inhalation of TRE or placebo from the relative changes of hemodynamic parameters (means±95% confidence intervals). PVR, pulmonary vascular resistance; PAP, mean pulmonary arterial pressure; SAP, mean systemic arterial pressure; SVR, systemic vascular resistance.

FIG. 10 presents hemodynamic responses to the inhalation of 15 µg treprostinil. The inhalation time by increasing treprostinil concentration. A pulse of aerosol was generated every 6 seconds. TRE aerosol was inhaled in concentrations of 100 µg/ml (18 pulses; n=6), 200 µg/ml (9 pulses; n=6), 600 µg/ml (3 pulses; n=21), 1000 µg/ml (2 pulses; n=7) and 2000 µg/ml (1 pulse; n=8). Placebo data correspond to FIG. 8. Data are shown as means±95% confidence intervals. PVR, pulmonary vascular resistance; PAP, mean pulmonary arterial pressure; SAP, mean systemic arterial pressure; CO, cardiac output.

FIG. 11 presents areas between the placebo curve and the responses to 15 µg treprostinil applied at increasing concentrations to minimize inhalation time. Mean±SEM of relative changes of hemodynamic parameters (observation time 120 min). PAP, pulmonary arterial pressure, SAP, systemic arterial pressure, PVR, pulmonary vascular resistance, CO, cardiac output, SaO₂, systemic arterial oxygen saturation, SvO₂, pulmonary arterial oxygen saturation.

FIG. 12 presents pharmacokinetics of treprostinil after a single inhalation. Treprostinil plasma levels after inhalation of 30 µg, 60 µg, 90 µg or 120 µg treprostinil (6 min inhalation period; experiments correspond to those shown in FIGS. 8 and 9). Data with error bars represent mean values±SEM.

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DETAILED DESCRIPTION OF THE INVENTION

Unless otherwise specified, the term “a” or “an” used herein shall mean “one or more.”

The present application incorporates herein by reference in its entirety Voswinckel R, et al. J. Am. Coll. Cardiol. 2006; 48:1672-1681.

The inventors discovered that a therapeutically effective dose of treprostinil can be administered in a few single inhalations using a compact inhalation device, such as a metered dose inhaler. Furthermore, the inventors discovered that such administering does not cause significant side effects, especially no significant side effects related to systemic blood pressure and circulation as well as no gas exchange deteriorations or disruptions.

Accordingly, one embodiment of the invention is a method of delivering to a subject in need thereof, such as a human being, a therapeutically effective amount of treprostinil comprising administering to the subject a formulation comprising a therapeutically effective amount of treprostinil, its derivative or a pharmaceutically acceptable salt thereof using a metered dose inhaler. Treprostinil can be administered via a metered dose inhaler to a subject affected with a condition or disease, which can be treated by treprostinil, such as asthma, pulmonary hypertension, peripheral vascular disease or pulmonary fibrosis.

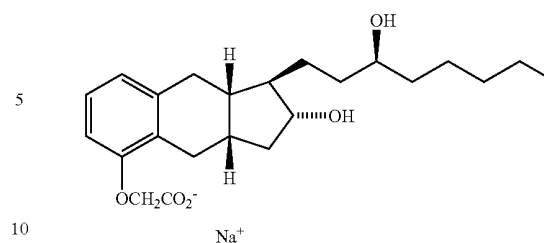
Another embodiment of the invention is a method for treating pulmonary hypertension, comprising administering to a subject in need thereof, such as a human being, treprostinil or its derivative, or a pharmaceutically acceptable salt using a metered dose inhaler.

Treprostinil, or 9-deoxy-2',9- α -methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)-13,14-dihydro-prostaglandin F₁, is a prostacyclin analogue, first described in U.S. Pat. No. 4,306,075. U.S. Pat. No. 5,153,222 describes use of treprostinil for treatment of pulmonary hypertension. Treprostinil is approved for the intravenous as well as subcutaneous route, the latter avoiding septic events associated with continuous intravenous catheters. U.S. Pat. Nos. 6,521,212 and 6,756,033 describe administration of treprostinil by inhalation for treatment of pulmonary hypertension, peripheral vascular disease and other diseases and conditions. U.S. Pat. No. 6,803,386 discloses administration of treprostinil for treating cancer such as lung, liver, brain, pancreatic, kidney, prostate, breast, colon and head-neck cancer. US patent application publication No. 2005/0165111 discloses treprostinil treatment of ischemic lesions. U.S. Pat. No. 7,199,157 discloses that treprostinil treatment improves kidney functions. US patent application publication No. 2005/0282903 discloses treprostinil treatment of neuropathic foot ulcers. U.S. provisional application No. 60/900,320 filed Feb. 9, 2007, discloses treprostinil treatment of pulmonary fibrosis.

The term “acid derivative” is used herein to describe C1-4 alkyl esters and amides, including amides wherein the nitrogen is optionally substituted by one or two C1-4 alkyl groups.

The present invention also encompasses methods of using Treprostinil or its derivatives, or pharmaceutically acceptable salts thereof. In one embodiment, a method uses Treprostinil sodium, currently marketed under the trade name of REMODULIN®. The FDA has approved Treprostinil sodium for the treatment of pulmonary arterial hypertension by injection of dose concentrations of 1.0 mg/mL, 2.5 mg/mL, 5.0 mg/mL and 10.0 mg/mL. The chemical structure formula for Treprostinil sodium is:

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Treprostinil sodium is sometimes designated by the chemical names: (a) [(1R,2R,3aS,9aS)-2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[*f*]inden-5-yl]oxy]acetic acid; or (b) 9-deoxy-2',9- α -methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)-13,14-dihydro-prostaglandin F₁. Treprostinil sodium is also known as: UT-15; LRX-15; 15AU81; UNIPROST™; BW A15AU; and U-62,840. The molecular weight of Treprostinil sodium is 390.52, and its empirical formula is C₂₃H₃₄O₅.

In certain embodiments, treprostinil can be administered in combination with one or more additional active agents. In some embodiments, such one or more additional active agents can be also administered together with treprostinil using a metered dose inhaler. Yet in some embodiments, such one or more additional active agents can be administered separately from treprostinil. Particular additional active agents that can be administered in combination with treprostinil may depend on a particular disease or condition for treatment or prevention of which treprostinil is administered. In some cases, the additional active agent can be a cardiovascular agent such as a calcium channel blocker, a phosphodiesterase inhibitor, an endothelial antagonist, or an antiplatelet agent.

The present invention extends to methods of using physiologically acceptable salts of Treprostinil, as well as non-physiologically acceptable salts of Treprostinil that may be used in the preparation of the pharmacologically active compounds of the invention.

The term “pharmaceutically acceptable salt” refers to a salt of Treprostinil with an inorganic base, organic base, inorganic acid, organic acid, or basic or acidic amino acid. Salts of inorganic bases can be, for example, salts of alkali metals such as sodium or potassium; alkaline earth metals such as calcium and magnesium or aluminum; and ammonia. Salts of organic bases can be, for example, salts trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, and triethanolamine. Salts of inorganic acids can be, for example, salts of hydrochloric acid, hydroboric acid, nitric acid, sulfuric acid, and phosphoric acid. Salts of organic acids can be, for example, salts of formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, lactic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, and *p*-toluenesulfonic acid. Salts of basic amino acids can be, for example, salts of arginine, lysine and ornithine. Salts of acidic amino acids can include, for example, salts of aspartic acid and glutamic acid. Quaternary ammonium salts can be formed, for example, by reaction with lower alkyl halides, such as methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides, with dialkyl sulphates, with long chain halides, such as decyl, lauryl, myristyl, and stearyl chlorides, bromides, and iodides, and with aralkyl halides, such as benzyl and phenethyl bromides.

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Preferred pharmaceutically acceptable salts are disclosed, for example, in U.S. patent application publication No. 20050085540.

Treprostinil can be administered by inhalation, which in the present context refers to the delivery of the active ingredient or a combination of active ingredients through a respiratory passage, wherein the subject in need of the active ingredient(s) through the subject's airways, such as the subject's nose or mouth.

A metered dose inhaler in the present context means a device capable of delivering a metered or bolus dose of respiratory drug, such as treprostinil, to the lungs. One example of the inhalation device can be a pressurized metered dose inhaler, a device which produces the aerosol clouds for inhalation from solutions and/or suspensions of respiratory drugs in chlorofluorocarbon (CFC) and/or hydrofluoroalkane (HFA) solutions.

The inhalation device can be also a dry powder inhaler. In such case, the respiratory drug is inhaled in solid formulation, usually in the form of a powder with particle size less than 10 micrometers in diameter or less than 5 micrometers in diameter.

The metered dose inhaler can be a soft mist inhaler (SMI), in which the aerosol cloud containing a respiratory drug can be generated by passing a solution containing the respiratory drug through a nozzle or series of nozzles. The aerosol generation can be achieved in SMI, for example, by mechanical, electromechanical or thermomechanical process. Examples of soft mist inhalers include the Respimat® Inhaler (Boeinger Ingelheim GmbH), the AERx® Inhaler (Aradigm Corp.), the Mystic™ Inhaler (Ventaira Pharmaceuticals, Inc) and the Aira™ Inhaler (Chrysalis Technologies Incorporated). For a review of soft mist inhaler technology, see e.g. M. Hindle, The Drug Delivery Companies Report, Autumn/Winter 2004, pp. 31-34. The aerosol for SMI can be generated from a solution of the respiratory drug further containing pharmaceutically acceptable excipients. In the present case, the respiratory drug is treprostinil, its derivative or a pharmaceutically acceptable salt thereof, which can be formulated in SMI as a solution. The solution can be, for example, a solution of treprostinil in water, ethanol or a mixture thereof. Preferably, the diameter of the treprostinil-containing aerosol particles is less than about 10 microns, or less than about 5 microns, or less than about 4 microns.

Treprostinil concentration in an aerosolable formulation, such as a solution, used in a metered dose inhaler can range from about 500 µg/ml to about 2500 µg/ml, or from about 800 µg/ml to about 2200 µg/ml, or from about 1000 µg/ml to about 2000 µg/ml.

The dose of treprostinil that can be administered using a metered dose inhaler in a single event can be from about 15 µg to about 100 µg or from about 15 µg to about 90 µg or from about 30 µg to about 90 µg or from about 30 µg to about 60 µg.

Administering of treprostinil in a single event can be carried out in a limited number of breaths by a patient. For example, treprostinil can be administered in 20 breaths or less, or in 10 breaths or less, or than 5 breaths or less. Preferably, treprostinil is administered in 3, 2 or 1 breaths.

The total time of a single administering event can be less than 5 minutes, or less than 1 minute, or less than 30 seconds.

Treprostinil can be administered a single time per day or several times per day.

In some embodiments, the method of treatment of pulmonary hypertension can further comprise administering at least one supplementary agent selected from the group consisting of sildenafil, tadalafil, calcium channel blockers (diltiazem, amlodipine, nifedipine), bosentan, sitaxsentan, ambrisentan,

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and pharmaceutically acceptable salts thereof. In some embodiments, the supplementary agents can be included in the treprostinil formulation and, thus, can be administered simultaneously with treprostinil using a metered dose inhaler. In some embodiments, the supplementary agents can be administered separately from treprostinil. In some embodiments, the application of intravenous prostacyclin (flolan), intravenous iloprost or intravenous or subcutaneous treprostinil can be administered in addition to treprostinil administered via inhalation using a metered dose inhaler.

The present invention also provides a kit that includes a metered dose inhaler containing a pharmaceutical formulation comprising treprostinil or its derivative, or a pharmaceutically acceptable salt thereof. Such a kit can further include instructions on how to use the metered dose inhaler for inhaling treprostinil. Such instructions can include, for example, information on how to coordinate patient's breathing, and actuation of the inhaler. The kit can be used by a subject, such as human being, affected with a disease or condition that can be treated by treprostinil, such as asthma, pulmonary hypertension, peripheral vascular disease or pulmonary fibrosis.

In some cases, the kit is a kit for treating pulmonary hypertension, that includes (i) a metered dose inhaler containing a pharmaceutical formulation comprising treprostinil or its derivative, or a pharmaceutically acceptable salt thereof; and (ii) instructions for use of the metered dose inhaler containing treprostinil in treating pulmonary hypertension.

As used herein, the phrase "instructions for use" shall mean any FDA-mandated labeling, instructions, or package inserts that relate to the administration of Treprostinil or its derivatives, or pharmaceutically acceptable salts thereof, for treatment of pulmonary hypertension by inhalation. For example, instructions for use may include, but are not limited to, indications for pulmonary hypertension, identification of specific symptoms associated with pulmonary hypertension, that can be ameliorated by Treprostinil, recommended dosage amounts for subjects suffering from pulmonary hypertension and instructions on coordination of individual's breathing and actuation of the metered dose inhaler.

The present invention can be illustrated in more detail by the following example, however, it should be understood that the present invention is not limited thereto.

EXAMPLE 1

Open Label Study Upon Acute Safety, Tolerability and Hemodynamic Effects of Inhaled Treprostinil Delivered in Seconds

A study was conducted of acute vasodilator challenge during right heart catheter investigation to determine the safety, tolerability and pulmonary vasodilatory potency of inhaled treprostinil applied in seconds by a soft mist inhaler (SMI-TRE). The study produced evidence for a long lasting favourable effect of SMI-TRE on pulmonary hemodynamics in absence of systemic side effects and gas exchange disruptions.

Summary

Inhaled nitric oxide (20 ppm; n=45) and inhaled treprostinil sodium (TRE; n=41) or placebo (n=4) were applied once during right heart catheter investigation. TRE was delivered in 2 breaths (1000 µg/ml aerosol concentration; 30 µg dose; n=12), 3 breaths (1000 µg/ml; 45 µg; n=9) or 2 breaths (2000 µg/ml; 60 µg; n=20) from a Respimat® SMI. Pulmonary hemodynamics and blood gases were measured at defined time points, observation time following TRE application was 120 minutes. TRE doses of 30 µg, 45 µg and 60 µg reduced

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pulmonary vascular resistance (PVR) to $84.4 \pm 8.7\%$, $71.4 \pm 17.5\%$ and $77.5 \pm 7.2\%$ of baseline values, respectively (mean $\pm 95\%$ confidence interval). The 120 minute area under the curve for PVR for placebo, 30 μg , 45 μg and 60 μg TRE was 1230 ± 1310 , -870 ± 940 , -2450 ± 2070 and -2000 ± 900 min %, respectively. Reduction of PVR by a single inhalation of the two higher doses outlasted the observation period of 120 minutes. Reduction of systemic vascular resistance and pressure was negligible, showing a high pulmonary selectivity for SMI-TRE. Intrapulmonary selectivity was also provided by SMI-TRE as ventilation/perfusion matching, assessed by the multiple inert gas elimination technique in 5 patients with gas exchange problems, was not significantly different after SMI-TRE compared to inhaled nitric oxide or no treatment. No significant side effects were observed.

Conclusions: The acute application of inhaled treprostinil with a metered dose inhaler in 2-3 breaths was safe, well tolerated and induced a strong and sustained pulmonary selective vasodilation.

Methods and Patients

A total number of 45 patients with moderate to severe precapillary pulmonary hypertension were enrolled. Patient characteristics were: female to male ratio (f/m)=29/16, age 59 ± 2.3 years, pulmonary artery pressure (PAP) 45 ± 1.8 mmHg, pulmonary vascular resistance (PVR) 743 ± 52 dynes $\cdot\text{s}\cdot\text{cm}^{-5}$, pulmonary artery wedge pressure (PAWP) 8.6 ± 0.5 mmHg, central venous pressure (CVP) 6.4 ± 0.7 mmHg, cardiac output (CO) 4.5 ± 0.2 l/min, central venous oxygen saturation (SvO₂) 62.3 ± 1.2 mmHg (mean \pm Standard Error of the Mean). Disease etiologies were idiopathic PAH (iPAH) (n=13), PAH other (n=11), chronic thromboembolic pulmonary hypertension (CTEPH) (n=17) and pulmonary fibrosis (n=4). Table 1 presents the patient characteristics of the different groups.

TABLE 1

Patient characteristics of the different treatment groups.				
	Placebo (n = 4)	30 μg TRE (n = 12)	45 μg TRE (n = 9)	60 μg TRE (n = 20)
Age [years]	61 ± 8	53.9 ± 3.9	54.2 ± 5.7	65.5 ± 3.1
PAP [mmHg]	49.5 ± 10.1	45 ± 3.1	54.3 ± 2.8	39.7 ± 2.0
PVR [Dynes]	896 ± 163	597 ± 53.9	1049 ± 107	663 ± 81
CO [l/min]	4.46 ± 0.9	5.2 ± 0.4	3.9 ± 0.4	4.4 ± 0.3
SAP [mmHg]	98 ± 8.1	90.1 ± 3.2	82.8 ± 3.9	86.1 ± 2.0
SaO ₂ [%]	85.3 ± 4.5	90.0 ± 1.1	89.6 ± 1.1	90.6 ± 0.5
SvO ₂ [%]	57.5 ± 3.9	66.0 ± 1.6	59.1 ± 3.4	62.5 ± 1.6

Data are given as mean \pm Standard Error of the Mean (SEM). PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; CO = cardiac output; SAP = systemic arterial pressure; SaO₂ = arterial oxygen saturation; SvO₂ = central venous oxygen saturation.

Baseline values were determined 20-30 minutes after placement of the catheter. Heart rate, pulmonary and systemic blood pressure and cardiac output were measured and blood gases were taken during each pharmacological intervention at defined time points. Pharmacological interventions included the inhalation of 20 ppm nitric oxide (NO) after evaluation of baseline parameters (n=45) and the consecutive inhalation of placebo (n=4), 30 μg SMI-TRE (n=12), 45 μg SMI-TRE (n=9) or 60 μg (n=20) SMI-TRE. Placebo and treprostinil was applied with the RespiMAT® SMI. For filling of this device with treprostinil sodium, the placebo solution was withdrawn from the device with a syringe and treprostinil solution was injected into the device under sterile conditions. Aerosol quality was controlled before and after refilling of the SMI

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devices by laser diffractometry, see e.g. Gessler T., Schmehl T., Hoepfer M. M., Rose F., Ghofrani H. A., Olschewski H. et al. Ultrasonic versus jet nebulization of iloprost in severe pulmonary hypertension. *Eur. Respir. J.* 2001; 17:14-19 incorporated herein in its entirety. The aerosol sizes before (placebo) and after filling (treprostinil) were unchanged. The aerosol particles mass median aerodynamic diameter of treprostinil-aerosol was 4-5 μm , which can be at the upper limit for alveolar deposition. The aerosol volume delivered by one cycle from the SMI was 15 μl . The solution used for aerosol generation was prepared from treprostinil sodium salt using a standard protocol. The SMI was either filled with a concentration of 1000 $\mu\text{g}/\text{ml}$ treprostinil sodium (one aerosol puff=15 μg TRE) or with 2000 $\mu\text{g}/\text{ml}$ (one puff=30 μg TRE). The different doses were applied as 2 puffs 1000 $\mu\text{g}/\text{ml}$ (30 μg), 3 puffs 1000 $\mu\text{g}/\text{ml}$ (45 μg) and 2 puffs 2000 $\mu\text{g}/\text{ml}$ (60 μg). The placebo was inhaled as 2 puffs from a placebo-SMI. Hemodynamics and gas-exchange parameters were recorded for 120 minutes after TRE inhalation. This study used the RespiMAT® device, because the implemented "soft mist" technology was well suited for the deposition of such highly active drugs like prostanoids.

The impact of SMI-TRE on ventilation-perfusion matching was assessed in five patients (30 μg TRE, n=2; 45 μg TRE, n=1; 60 μg TRE, n=2) with pre-existing gas exchange problems by use of the multiple inert gas elimination technique (MIGET), see e.g. Wagner P D, Saltzman H A, West J B. Measurement of continuous distributions of ventilation-perfusion ratios: theory. *J Appl Physiol.* 1974; 36:588-99; Ghofrani H A, Wiedemann R, Rose F, Schermuly R T, Olschewski H, Weissmann N et al. Sildenafil for treatment of lung fibrosis and pulmonary hypertension: a randomised controlled trial. *Lancet.* 2002; 360:895-900, both incorporated herein in their entirety.

Statistics:

Mean values, standard deviation, standard error of the mean and 95% confidence intervals were calculated. Statistical analysis was done by use of a paired t-test.

Results:

The inhalation of treprostinil sodium from the metered dose inhaler (SMI-TRE) was well tolerated, only mild and transient cough for a maximum of one minute was reported. No systemic side effects like headache, flush, nausea or dizziness were observed.

Two to three breaths of SMI-TRE induced a strong pulmonary vasodilation that outlasted the observation time of 120 minutes (45 and 60 μg). The lower dose of 30 μg TRE induced a somewhat shorter effect on pulmonary vascular resistance; however, the maximal pulmonary vasodilation was comparable. In contrast, placebo inhalation did not induce pulmonary vasodilation. In fact a slight increase in PVR over the time of the right heart catheter investigation could be recorded following placebo inhalation (FIG. 1). The effect of SMI-TRE on systemic vascular resistance and pressure was very small and not clinically significant. Cardiac output was significantly increased over the whole observation period, whereas heart rate was rather unchanged. Gas exchange was not influenced by SMI-TRE (FIG. 2). The maximal changes in hemodynamic and gas-exchange parameters compared to baseline values are depicted in Table 2.

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TABLE 2

Extremes of the relative changes of hemodynamic and gas exchange parameters compared to baseline after inhalation of Placebo (n = 4), 30 µg treprostinil (n = 12), 45 µg treprostinil (n = 9) and 60 µg treprostinil (n = 20).				
	Placebo	30 µg TRE	45 µg TRE	60 µg TRE
PAP (min)	99.4 ± 3.0	83.4 ± 3.2	77.6 ± 6.8	79.5 ± 2.4
PVR (min)	101.4 ± 1.9	84.4 ± 4.4	71.4 ± 8.9	77.5 ± 3.7
CO (max)	99.7 ± 1.1	108.8 ± 3.8	108.6 ± 5.6	103.8 ± 2.0
SVR (min)	104.3 ± 4.3	97.7 ± 4.2	92 ± 3.9	91.3 ± 2.1
SAP (min)	102.7 ± 1.7	97.3 ± 1.9	96.1 ± 1.5	93.6 ± 2.9
HR (max)	105 ± 2.1	106.1 ± 2.9	99.1 ± 2.4	101.1 ± 0.9
SaO ₂ (min)	98.2 ± 0.4	101 ± 0.3	94.4 ± 1.8	95.8 ± 0.9
SvO ₂ (max)	104.5 ± 1.4	102.4 ± 1.3	104.5 ± 4.4	102 ± 1.0

Highest (max) and lowest (min) values during the observation period are shown. Data are given as percent of baseline values (mean ± SEM). PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance; CO = cardiac output; SAP = systemic arterial pressure; HR = heart rate; SaO₂ = arterial oxygen saturation; SvO₂ = central venous oxygen saturation.

The areas under the curve for PVR were calculated for placebo and the different SMI-TRE doses over the 120 minute observation period (FIG. 3). A dose effect of SMI-TRE with a trend to a more sustained effect with the two highest doses could be observed.

The inhalation of a highly concentrated aerosol can be in theory prone to disturbances of gas exchange because the deposition of even small amounts of aerosol may deliver high doses locally and thereby antagonize the hypoxic pulmonary vasoconstriction in poorly ventilated areas. This would then lead to increased shunt flow or increase of low ventilation/perfusion (V/Q) areas. This question was addressed in five patients with the multiple inert gas elimination technique (MIGET), the gold-standard for intrapulmonary V/Q ratio determination. The MIGET patients were selected for pre-existing gas exchange limitations. Characteristics of these patients were: PAP 54.6±3.2 mmHg, PVR 892±88 dynes, SaO₂ 91.7±0.5%, SvO₂ 65.2±1.8%. Etiologies were iPAH (n=1), CTEPH (n=3), pulmonary fibrosis (n=1). The maximal relative reduction of SaO₂ after inhalation of SMI-TRE in these patients was -3.8±1.5% compared to baseline values. Shunt flow at baseline, NO-inhalation and 60 minutes after SMI-TRE was 6.4±4.3%, 5.4±3.0% and 8.3±3.4%, respectively (mean±95% confidence interval; FIG. 4).

No significant increase in low V/Q areas or shunt fraction after inhalation of SMI-TRE was observed, in fact the distribution of perfusion was not different to that at baseline and during nitric oxide inhalation. This proves an excellent intrapulmonary selectivity of SMI-TRE, which is also reflected by unchanged arterial oxygen saturation.

Conclusion:

Treprostinil is tolerated at high doses with no systemic side effects. The application of an effective amount of treprostinil in only few or even one single breath was achieved with a highly concentrated treprostinil sodium solution. Treprostinil can be applied by a metered dose inhaler, such as Respimat® soft mist inhaler.

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EXAMPLE 2

Investigation of The Effects of Inhaled Treprostinil on Pulmonary Hemodynamics and Gas Exchange in Severe Pulmonary Hypertension

This study investigated the effects of inhaled treprostinil on pulmonary vascular resistance in severe pulmonary hypertension and addressed systemic effects and gas exchange as well as tolerability and efficacy of high doses of treprostinil given in short time. A total of 123 patients with a mean pulmonary artery pressure of about 50 mmHg were investigated in three separate randomized studies. Inhaled treprostinil exerted potent sustained pulmonary vasodilation with excellent tolerability and could be safely applied in a few breaths or even one breath.

Summary:

Three different studies were conducted on a total of 123 patients by means of right heart catheterization: i) a randomized crossover-design study (44 patients), ii) a dose escalation study (31 patients) and iii) a study of reduction of inhalation time while keeping the dose fixed (48 patients). The primary endpoint was the change in pulmonary vascular resistance (PVR).

The mean pulmonary artery pressure of the enrolled patients was about 50 mmHg. Hemodynamics and patient characteristics were similar in all studies. In study i) TRE and Iloprost (ILO), at an inhaled dose of 7.5 µg, displayed comparable PVR decrease, with a significantly different time course (p<0.001), TRE exhibiting a more sustained effect on PVR (p<0.0001) and less systemic side effects. In study ii) placebo, 30 µg, 60 µg, 90 µg or 120 µg TRE were applied with drug effects being observed for 3 hours after inhalation. A near-maximal acute PVR decrease was observed at 30 µg TRE. In study iii) TRE was inhaled with a pulsed ultrasonic nebulizer, mimicking a metered dose inhaler. 15 µg TRE was inhaled with 18 pulses (TRE concentration 100 µg/ml), 9 pulses (200 µg/ml), 3 pulses (600 µg/ml), 2 pulses (1000 µg/ml) or 1 pulse (2000 µg/ml), each mode achieving comparable, sustained pulmonary vasodilation.

Inhaled treprostinil exerts sustained pulmonary vasodilation with excellent tolerability at doses, which may be inhaled in a few or even one breath. Inhaled treprostinil is advantageous to inhaled iloprost in terms of duration of effect and systemic side effects. Inhaled treprostinil is well tolerated in concentrations up to 2000 mg/ml (bringing down inhalation time to a single breath) and in high doses (up to 90 µg).

Methods:

All inhalations were performed with the Optineb® ultrasonic nebulizer (Nebutech, Elsenfeld, Germany).

Study i) was a randomized, open-label, single-blind crossover study. The primary objective was to compare the acute hemodynamic effects and the systemic side effects of inhaled treprostinil with inhaled iloprost at comparable doses. A total number of 44 patients with moderate to severe precapillary pulmonary hypertension were enrolled. Patient characteristics and hemodynamic as well as gas exchange parameters are outlined in Table 3.

TABLE 3

Patient characteristics, hemodynamic parameters and gas exchange values at baseline, before challenge with inhalative prostanoids.											
	N	Age	Gender f/m	Etiology i/o/t/f	PAP [mmHg]	PVR [dyn*s*cm ⁻⁵]	SAP [mmHg]	CVP [mmHg]	PAWP [mmHg]	CO [l/min]	SaO ₂ [%]
1a	14	55.1 ± 4.8	11/3	4/4/2/4	53.8 ± 3.1	911 ± 102	95.4 ± 3.6	7.4 ± 1	8.0 ± 0.8	4.3 ± 0.4	93.8 ± 2
1b	14	54.1 ± 3.3	10/4	1/6/5/2	47.4 ± 3.8	716 ± 80	90.6 ± 3.3	5.9 ± 1.4	6.4 ± 0.7	4.7 ± 0.4	92 ± 1

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TABLE 3-continued

Patient characteristics, hemodynamic parameters and gas exchange values at baseline, before challenge with inhalative prostanoids.												
N	Age	Gender f/m	Etiology i/o/t/f	PAP [mmHg]	PVR [dyn*s*cm ⁻⁵]	SAP [mmHg]	CVP [mmHg]	PAWP [mmHg]	CO [l/min]	SaO ₂ [%]	SvO ₂ [%]	
1c	16	56 ± 2.9	7/9	6/3/6/1	47.5 ± 4.5	777 ± 102	92 ± 4.5	8.3 ± 1.4	8.6 ± 1.4	4.4 ± 0.5	91.4 ± 0.9	59.8 ± 2.6
2a	8	60.8 ± 4	4/4	2/2/3/1	51.9 ± 4.9	849 ± 152	95.9 ± 4.8	7.6 ± 1.4	11.1 ± 1.7	4.4 ± 0.6	89.6 ± 2.8	60.1 ± 2.8
2b	8	52.8 ± 6.6	6/2	1/3/3/1	49 ± 4	902 ± 189	92.4 ± 2.4	4.8 ± 1.1	7.2 ± 1.3	4.0 ± 0.4	92.4 ± 2.4	62.5 ± 1.7
2c	6	56.8 ± 5.9	4/2	0/2/2/2	44.2 ± 3.5	856 ± 123	96.3 ± 3.9	5 ± 1.1	6 ± 1	3.8 ± 0.3	92.8 ± 1.5	63.6 ± 1.8
2d	6	51.2 ± 3.8	4/2	2/2/2/0	55.5 ± 4.9	940 ± 110	91.2 ± 8.1	11.2 ± 1.2	10 ± 0.7	3.9 ± 0.4	92 ± 1.9	62 ± 5.8
2e	3	57.3 ± 9.1	1/2	0/1/0/2	45.3 ± 5.2	769 ± 267	99 ± 3.2	5 ± 2.1	9 ± 0.6	4.5 ± 0.6	94.2 ± 1.3	66.3 ± 1.5
3a	6	52.7 ± 6.6	4/2	2/4/0/0	53.8 ± 6.7	928 ± 145	92.7 ± 7.9	8.7 ± 2.7	8.8 ± 1.3	4.2 ± 0.6	90.4 ± 2.8	64.8 ± 4.3
3b	6	58.3 ± 3.5	4/2	3/1/1/1	54.2 ± 6.1	808 ± 156	94.3 ± 2.8	7 ± 1.4	10 ± 1.3	5 ± 0.7	91.9 ± 0.7	63.5 ± 2.9
3c	21	57.4 ± 5.6	8/3	7/7/6/1	46.1 ± 2.5	900 ± 99	88 ± 2.8	9 ± 1.4	9.2 ± 0.5	3.7 ± 0.3	91.7 ± 0.5	59.7 ± 2
3d	7	55.6 ± 5.8	3/4	0/4/3/0	53.1 ± 7.1	732 ± 123	91.4 ± 5.6	7.9 ± 3.1	8.6 ± 1.3	5 ± 0.4	90.7 ± 1.4	61.3 ± 3.7
3e	8	59 ± 5.2	7/1	0/4/4/0	45.1 ± 3.9	733 ± 114	92.8 ± 6.8	4.6 ± 0.8	8.1 ± 1.1	4.3 ± 0.2	90.7 ± 0.8	66.3 ± 2.8

Group 1 corresponds to study i); randomized crossover study comparing inhaled iloprost (ILO) and inhaled treprostinil (TRE). a = 7.5 g ILO vs. 7.5 µg TRE, b = 7.5 g ILO vs. 15 µg TRE (6 min inhalation time), c = 7.5 g ILO vs. 15 µg TRE (3 min inhalation time). Group 2 corresponds to study ii); evaluation of maximal tolerated dose of TRE. a = placebo inhalation, b = 30 µg TRE, c = 60 µg TRE, d = 90 µg TRE, e = 120 µg TRE. Group 3 corresponds to study iii); reduction of inhalation time by increase of TRE concentration, aiming at a total inhaled dose of 15 µg, a = 18 pulses of 100 µg/ml TRE, b = 9 pulses of 200 µg/ml TRE, c = 3 pulses of 600 µg/ml TRE, d = 2 pulses of 1000 µg/ml TRE, e = 1 pulse 2000 µg/ml TRE. Etiology of pulmonary hypertension was classified as idiopathic PAH (i), PAH of other causes (o), chronic thromboembolic PH (t), and pulmonary fibrosis (f).

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Each patient inhaled both iloprost and treprostinil on the same day during right heart catheter investigation; the drugs were administered consecutively with a one hour interval between the drug applications. One half of the study patients initially inhaled treprostinil and then inhaled iloprost (n=22), while the other half initially inhaled iloprost and then inhaled treprostinil (n=22). Patients were randomized to one of the two groups and blinded as to the study drugs. Drug effects were monitored for 60 minutes after each inhalation. Iloprost was inhaled at 4 µg/ml (6 min inhalation time; n=44) and treprostinil was inhaled at a concentration of 4 µg/ml (6 min inhalation; n=14), 8 µg/ml (6 min inhalation; n=14) or 16 µg/ml (3 min inhalation; n=16). Based on previous biophysical characterization of the ultrasonic device with iloprost- and treprostinil-solution, this corresponds to a total inhaled dose of 7.5 µg iloprost and treprostinil (4 µg/ml) and 15 µg treprostinil (8 µg/ml and 16 µg/ml), respectively.

Study ii) was a randomized, open-label, single blind, placebo controlled study. The primary objectives were to describe the pharmacodynamic and pharmacokinetic effects of inhaled treprostinil at a well tolerated dose (30 µg) and to explore the highest tolerated single dose. A total number of 31 patients inhaled either placebo or treprostinil; each patient received one inhalation. The first 16 patients were randomized to 30 µg TRE (16 µg/ml, n=8) or placebo (stock solution in a concentration corresponding to TRE 16 µg/ml). Subsequent patients received 60 µg TRE (32 µg/ml; n=6), 90 µg TRE (48 µg/ml; n=6) and 120 µg TRE (64 µg/ml; n=3). Inhalation time was 6 minutes in all groups. Hemodynamics and gas-exchange as well as arterial treprostinil concentrations were recorded for 180 minutes.

Study iii) was a randomized, open-label, single blind study. The primary objective was to explore the shortest possible inhalation time for a 15 µg dose of inhaled treprostinil. A total of 48 patients inhaled one dose of TRE during right heart catheter investigation. The drug was applied in 18, 9, 3, 2 or 1 breaths. The aerosol was generated by a pulsed ultrasonic nebulizer (VENTA-NEB®, Nebutech, Elsenfeld, Germany) in cycles consisting of 2 seconds aerosol production (pulse) and 4 seconds pause. The device included an opto-acoustical trigger for the patient to synchronize the inspiration to the end of the aerosol pulse, thereby providing exact dosage. The TRE dose of 15 µg was either generated during 18 cycles Optineb filled with 100 µg/ml TRE, n=6, 9 cycles (200 µg/ml TRE, n=6), 3 cycles (600 µg/ml TRE, n=21), 2 cycles (1000 µg/ml TRE, n=7) or 1 cycle (2000 µg/ml TRE, n=8). Hemodynamics and gas exchange were recorded for 120-180 minutes.

Treprostinil plasma concentrations were assessed in study ii) at 10, 15, 30, 60 and 120 minutes after inhalation. Treprostinil quantification was done by Alta Analytical Laboratory (El Dorado Hills, Calif., USA) with a validated liquid chromatography atmospheric-pressure ionization tandem mass spectrometry as previously described Wade M., et al. J. Clin. Pharmacol. 2004; 44:503-9. Mixed venous blood was drawn at the depicted time points (FIG. 11) after inhalation, centrifuged and the plasma frozen at -80° C. until temperature controlled shipping on dry ice.

Statistics:

For statistical analysis of study i) the repeated PVR measurements after inhaled iloprost and treprostinil were subjected to a three-factorial analysis of variance (ANOVA; factors: time (A), drug (B), treprostinil concentration (C)) to avoid multiple testing. The time to maximum PVR decrease after inhalation of iloprost versus treprostinil was compared by paired t-test. Area under the curve (AUC) was calculated from start of inhalation until 60 min after inhalation. Means, standard error of the mean (SEM) and 95% confidence intervals were calculated. For study ii) and iii) areas between curves (ABC) were calculated between placebo inhalation (study ii) and the respective treprostinil inhalation until 180 min (study ii) and 120 min (study iii) after end of inhalation. Results:

The inhalation of iloprost as well as treprostinil in study i) resulted in a rapid decrease in PVR and PAP (FIG. 5-7). No significant differences were observed for the areas under the curve (AUC) of PVR decrease after inhalation of 7.5 µg TRE in 6 minutes (AUC -12.6±7.0%), 15 µg TRE in 6 minutes (AUC -13.3±3.2%) and 15 µg TRE in 3 minutes (AUC -13.6±4.3%). The AUC for PVR after the inhalation of 7.5 µg iloprost in 6 minutes was -7.7±3.7% (mean±95% confidence interval). An overview of the pooled data of treprostinil inhalation as compared to iloprost inhalation is given in FIG. 7. The maximum effect of iloprost and treprostinil on PVR was comparable but this effect was reached significantly later after treprostinil inhalation (18±2 min) compared to iloprost (8±1 min; mean±SEM, p<0.0001) and lasted considerably longer (after 60 min, PVR values in the treprostinil group had not yet returned to baseline). The increase in cardiac output was less acute but prolonged after treprostinil inhalation. Systemic arterial pressure (SAP) was unaffected by treprostinil inhalation, whereas a transient decrease was observed after iloprost inhalation. Iloprost and treprostinil did not affect gas exchange. Three-factorial ANOVA for PVR demonstrated a significant difference between repeated mea-

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surements after inhalation ($p_{(A)} < 0.0001$), no significant difference between drugs ($p_B = 0.1$), no difference between treprostinil concentrations ($p_{(C)} = 0.74$) and a significant drug x time interaction ($p_{(A \times B)} < 0.0001$). This translates into a significant effect of both drugs on PVR with comparable drug potency but a prolonged drug effect of treprostinil compared to iloprost.

In this study the occasionally observed mild side effects of iloprost inhalation at the given dose (transient flush, headache) were not observed with inhaled treprostinil. Bad taste was reported by most of the patients after inhalation of TRE. This was later found to be attributable to the metacresol preservative contained in the treprostinil solution.

In study ii) pharmacodynamics of inhaled placebo or treprostinil were observed for 180 minutes. Placebo inhalation was followed by a gradual increase in PVR over the entire observation time. Due to reduced patient numbers in the 120 μg TRE group (because of side effects, see below), the hemodynamic values for this group were not included in the graphs of this study (FIG. 8-9). All TRE doses lead to comparable maximal decreases of PVR to $76.5 \pm 4.7\%$ (30 μg), $73.7 \pm 5.8\%$ (60 μg), $73.3 \pm 4.3\%$ (90 μg) and $65.4 \pm 4.1\%$ (120 μg) of baseline values. An extended duration of pulmonary vasodilation was noted, surpassing the 3 hour observation period for the 60 μg and 90 μg (and 120 μg) TRE doses, whereas in the 30 μg dose group the hemodynamic changes had just returned to baseline within this period. Even at the highest doses, TRE had only minor effects on systemic arterial pressure (FIG. 8). Cardiac output was increased to a maximum of $106.8 \pm 3.2\%$ (30 μg), $122.9 \pm 4.3\%$ (60 μg), $114.3 \pm 4.8\%$ (90 μg) and $111.3 \pm 3.9\%$ (120 μg TRE). The areas between the response curves after placebo versus TRE inhalation were calculated for PVR, PAP, SVR and SAP (FIG. 9). Areas between the curves for PVR were not significantly different for 30 μg , 60 μg and 90 μg TRE, a nearly maximal effect on PVR was already observed with 30 μg TRE. Effects on PAP and SAP were small and did not show a dose-response relationship. Gas exchange was not affected at doses up to 90 μg TRE, but arterial oxygen saturation was significantly decreased at a dose of 120 μg TRE in all 3 patients. Further dose increments were omitted due to this side effect and severe headache in one patient.

Again, bad taste of the TRE aerosol was reported by most patients. Other side effects were flushing ($n=1$; 30 μg TRE), mild transient cough ($n=3$; 60 μg TRE), mild transient bronchoconstriction that resolved after one inhalation of fenoterol ($n=1$; 30 μg TRE), moderate bronchoconstriction that resolved after one inhalation of fenoterol ($n=1$; 120 μg TRE), and severe headache ($n=1$; 120 μg TRE). The bad taste, the bronchoconstriction and the drop in SaO_2 was attributed to metacresol in the original TRE solution. With the use of a metacresol-free solution of TRE (University Hospital Giesen, Germany; produced according to the manufacturer's protocol) in the following study, these side effects did no longer occur.

Study iii) was performed with metacresol-free TRE solution, having no specific taste and smell. A total of 48 patients were enrolled. This study aimed at the reduction of inhalation time and aerosol volume needed for pulmonary drug delivery. A modified Optineb inhalation device was programmed to produce a constant amount of aerosol during repeatable pulses of aerosol generation. With this device, treprostinil could be safely utilized up to a concentration of 2000 $\mu\text{g}/\text{ml}$ without considerable side effects. No relationship of number or type of side effects to TRE concentration was observed. Reported side effects were mild transient cough ($n=6$), mild headache ($n=2$) and mild jaw pain ($n=1$).

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The reduction of PVR and PAP was comparable between all groups (FIG. 10). TRE inhalation reduced PVR to $76.3 \pm 5.6\%$ (18 pulses, 100 $\mu\text{g}/\text{ml}$), $72.9 \pm 4.9\%$ (9 pulses, 200 $\mu\text{g}/\text{ml}$), $71.2 \pm 6.0\%$ (3 pulses, 600 $\mu\text{g}/\text{ml}$), $77.4 \pm 4.5\%$ (2 pulses, 1000 $\mu\text{g}/\text{ml}$) and $80.3 \pm 5.2\%$ (1 pulse, 2000 $\mu\text{g}/\text{ml}$). PAP was reduced to $84.2 \pm 4.5\%$ (18 pulses, 100 $\mu\text{g}/\text{ml}$), $84.2 \pm 4.1\%$ (9 pulses, 200 $\mu\text{g}/\text{ml}$), $81.1 \pm 4.1\%$ (3 pulses, 600 $\mu\text{g}/\text{ml}$), $86 \pm 4\%$ (2 pulses, 1000 $\mu\text{g}/\text{ml}$) and $88 \pm 5.4\%$ (1 pulse, 2000 $\mu\text{g}/\text{ml}$). Cardiac output was moderately increased in all groups, whereas systemic arterial pressure was not significantly affected.

The areas between the curves (ABC) for changes in hemodynamic and gas-exchange parameters after inhalation of 15 μg TRE versus placebo were calculated for an observation time of 120 minutes (FIG. 11). The ABC for both PVR and PAP was comparable between all groups.

Pharmacokinetic results from study ii): Peak plasma concentrations of treprostinil were found 10-15 minutes after inhalation. Maximal treprostinil plasma concentrations (C_{max}) for the 30 μg , 60 μg , 90 μg and 120 μg doses were 0.65 ± 0.28 ng/ml ($n=4$), 1.59 ± 0.17 ng/ml ($n=4$), 1.74 ng/ml ($n=1$) and 3.51 ± 1.04 ng/ml ($n=2$), respectively (mean \pm SEM; FIG. 12).

Discussion:

These studies investigated whether i) the acute effects of inhaled treprostinil would be comparable to or possibly advantageous over inhaled iloprost in pulmonary hypertensive patients, ii) the inhaled prostanoid dose might be increased without substantial local or systemic side effects, and iii) if the time of inhalation, which is 6-12 minutes for iloprost, could be reduced significantly by increasing the concentration of treprostinil aerosol.

The patient population in these studies included different forms of precapillary pulmonary hypertension. All these patients had a need for therapy of pulmonary hypertension and reflected the typical population of a pulmonary hypertension center. No major differences in patient characteristics or hemodynamic baseline values existed between the different groups (table 3).

In study i) it was shown that the inhalation of treprostinil and iloprost in similar doses resulted in a comparable maximum pulmonary vasodilatory effect. However, marked differences in the response profile were noted. The onset of the pulmonary vasodilatory effect of inhaled treprostinil was delayed compared to iloprost, but lasted considerably longer, with the PVR decrease continuing beyond the one-hour observation period. Although the average dose of treprostinil was higher than the iloprost dose, no systemic effects were noted after treprostinil inhalation, whereas flush and transient SAP decrease, accompanied by more prominent cardiac output increase, occurred after iloprost inhalation. Such side effects were more prominent than in previous studies with inhaled iloprost. This may have been caused by the fact that the iloprost dose used in this study was 50% higher than the recommended single inhalation dose (5 μg) and that the preceding treprostinil inhalation may have added to the systemic side effects caused by the iloprost inhalation. Surprisingly, with TRE there was no such systemic side effect, although the average effect on PVR was as potent as with iloprost.

This study used a cross-over design in order to minimize the effects of inter-individual differences in response to prostanoids. The short observation period of 1 hour was used to avoid an uncomfortably long catheter investigation. As a study limitation, the short observation interval may have caused carryover effects of the first to the second period as suggested by FIG. 5. However, this still allowed for the interpretation of the study, that both drugs are potent pulmonary

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vasodilators and that treprostinil effects are significantly sustained compared to the iloprost effects.

The longer duration of action and the virtual absence of side effects (except the bitter taste of treprostinil aerosol, later attributed to metacresol) encouraged increasing the applied treprostinil dose in study ii). Observation time was extended to 3 hours to obtain precise pharmacodynamic data. Inhaled treprostinil resulted in a strong pulmonary vasodilation that outlasted the observation time of 3 hours when compared to placebo inhalation. Surprisingly, inhaled treprostinil was tolerated in doses up to 90 µg.

Study iii) successfully demonstrated that the inhalation time could be reduced to literally one single breath of 2000 µg/ml treprostinil solution, thereby applying a dose of 15 µg. This drug administration with a single breath induced pulmonary vasodilation for longer than 3 hours compared to placebo inhalation. Side effects were minor, of low frequency and not related to drug concentration. It was a surprising finding that such high concentrations of treprostinil were so well tolerated.

Conclusion:

Inhaled treprostinil can be applied in high doses (up to 90 µg) with a minimal inhalation time. Inhaled treprostinil exerts high pulmonary selectivity and leads to a long-lasting pulmonary vasodilation.

Although the foregoing refers to particular preferred embodiments, it will be understood that the present invention is not so limited. It will occur to those of ordinary skill in the art that various modifications may be made to the disclosed embodiments and that such modifications are intended to be within the scope of the present invention.

All of the publications, patent applications and patents cited in this specification are incorporated herein by reference in their entirety.

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What is claimed is:

1. A method of treating pulmonary hypertension comprising:
 - administering by inhalation to a human suffering from pulmonary hypertension a therapeutically effective single event dose of a formulation comprising from 200 to 1000 µg/ml of treprostinil or a pharmaceutically acceptable salt thereof
 - with a pulsed ultrasonic nebulizer that aerosolizes a fixed amount of treprostinil or a pharmaceutically acceptable salt thereof per pulse,
 - said pulsed ultrasonic nebulizer comprising an opto-acoustical trigger which allows said human to synchronize each breath to each pulse,
 - said therapeutically effective single event dose comprising from 15 µg to 90 µg of treprostinil or a pharmaceutically acceptable salt thereof delivered in 1 to 18 breaths.
2. The method of claim 1, wherein the formulation comprises 600 µg/ml of the treprostinil or its pharmaceutically acceptable salt thereof.
3. The method of claim 1, wherein the single event dose is not repeated for a period of at least 3 hours.
4. The method of claim 1, wherein the single event dose produces a peak plasma concentration of treprostinil about 10-15 minutes after the single event dose.
5. The method of claim 1, wherein the fixed amount of treprostinil or its pharmaceutically salt for each breath inhaled by the human comprises at least 5 µg of treprostinil or its pharmaceutically acceptable salt.
6. The method of claim 2, wherein the fixed amount of treprostinil or its pharmaceutically salt for each breath inhaled by the human comprises at least 5 µg of treprostinil or its pharmaceutically acceptable salt.
7. The method of claim 1, wherein the single event dose is inhaled in 3-18 breaths by the human.
8. The method of claim 6, wherein the single event dose is inhaled in 3-18 breaths by the human.
9. The method of claim 6, wherein the single event dose is not repeated for a period of at least 3 hours.

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EXHIBIT 14

(12) **United States Patent**
Olschewski et al.

(10) **Patent No.:** **US 9,339,507 B2**
(45) **Date of Patent:** **May 17, 2016**

(54) **TREPROSTINIL ADMINISTRATION BY INHALATION**

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(52) **U.S. Cl.**

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(58) **Field of Classification Search**

CPC **A61K 31/557**; **A61K 9/008**
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See application file for complete search history.

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(57) **ABSTRACT**

Treprostinil can be administered using a metered dose inhaler. Such administration provides a greater degree of autonomy to patients. Also disclosed are kits that include a metered dose inhaler containing a pharmaceutical formulation containing treprostinil.

9 Claims, 12 Drawing Sheets

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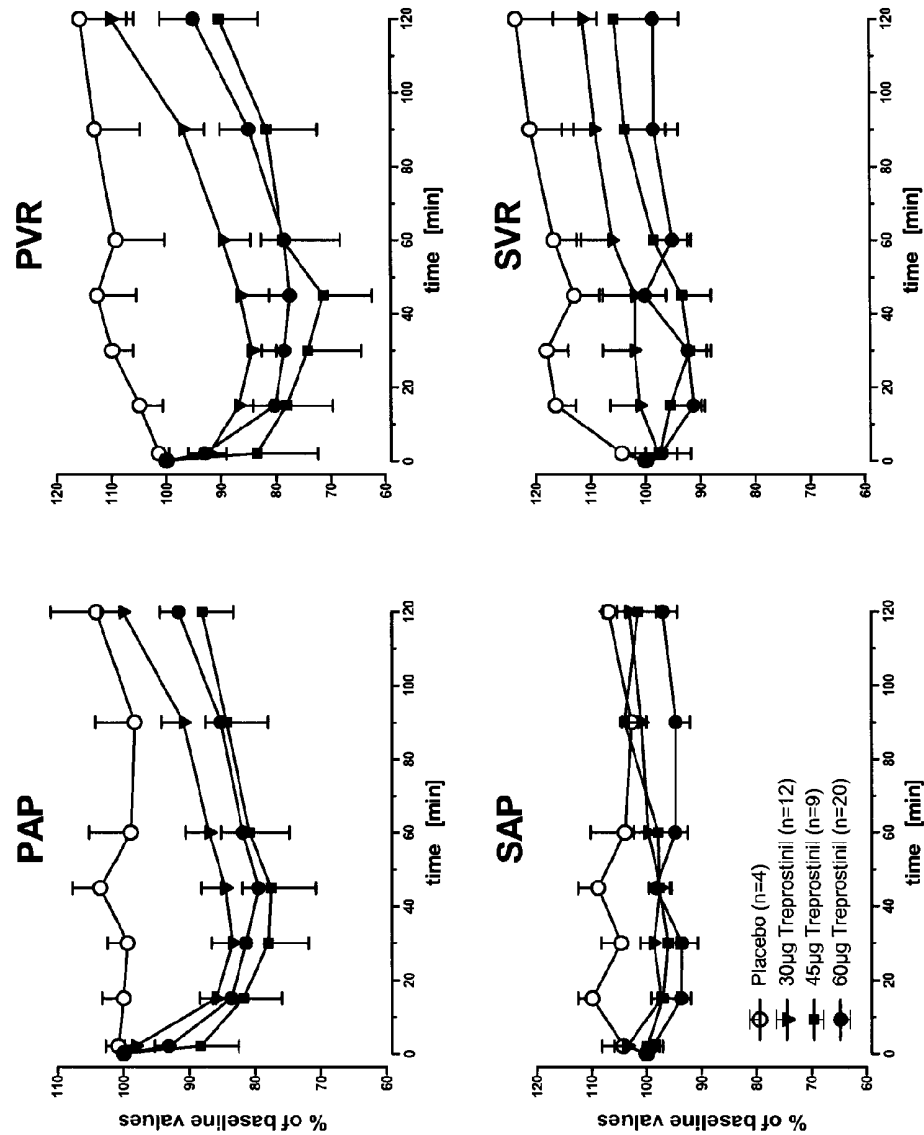
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FIGURE 1



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FIGURE 2

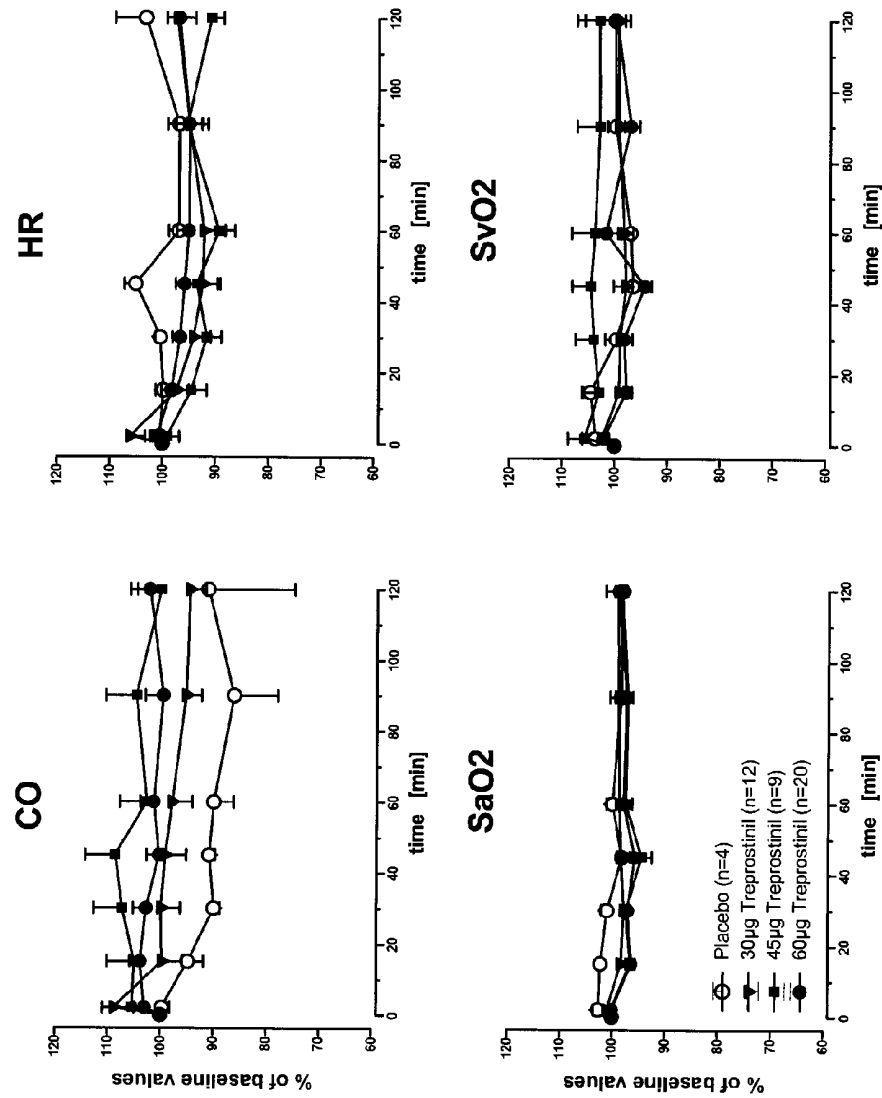


FIGURE 3

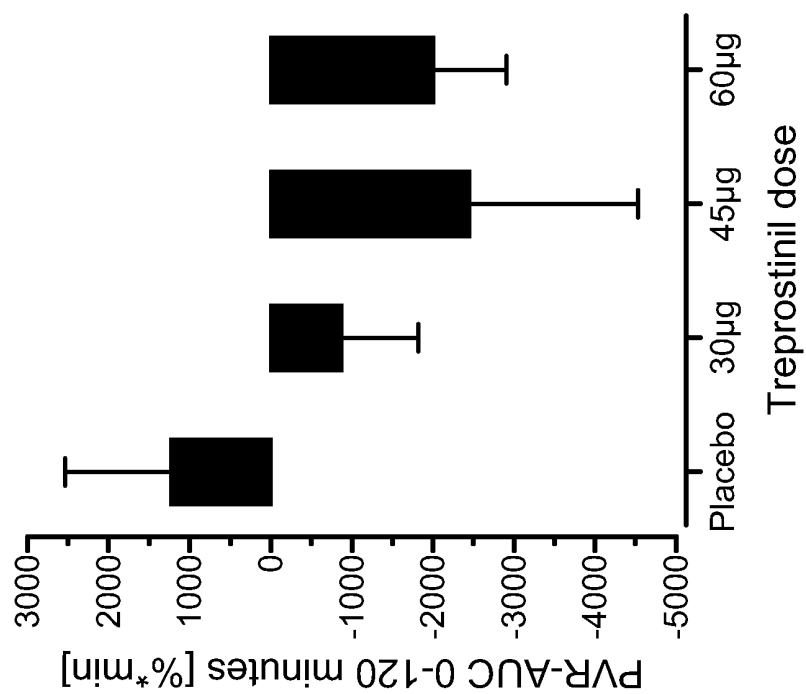
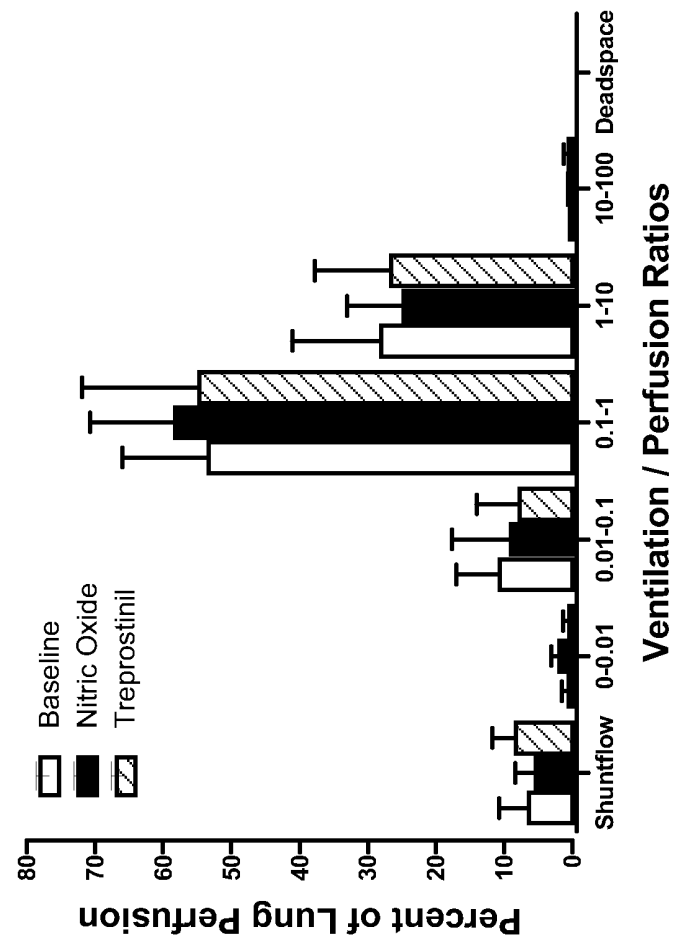


FIGURE 4



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FIGURE 5

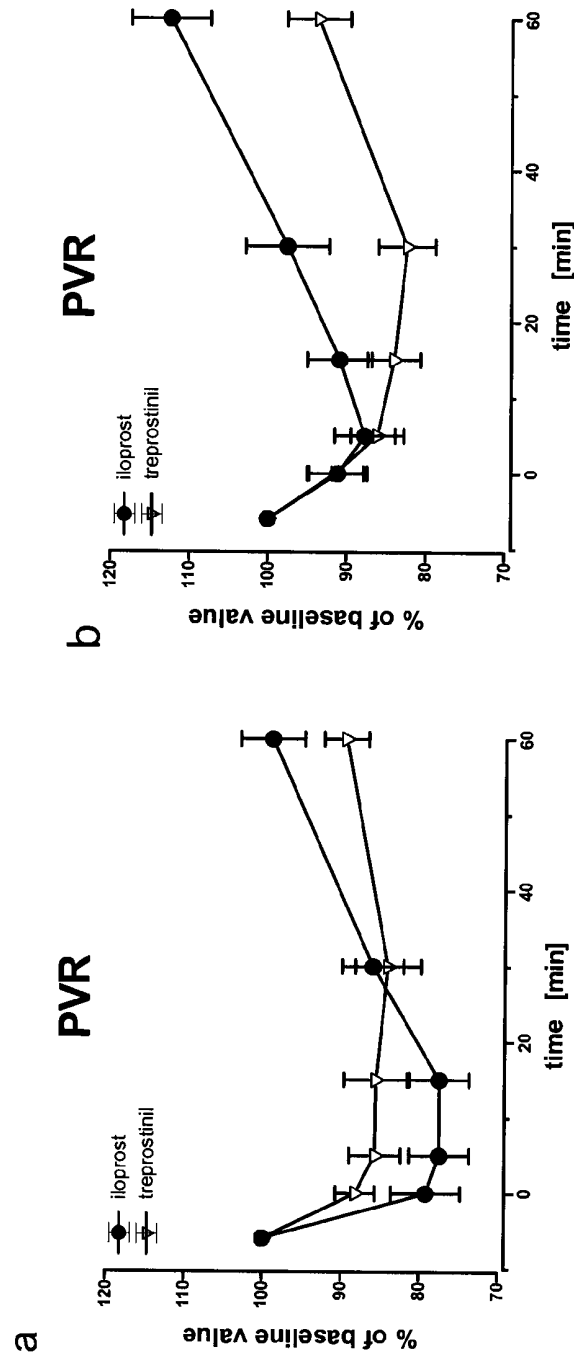
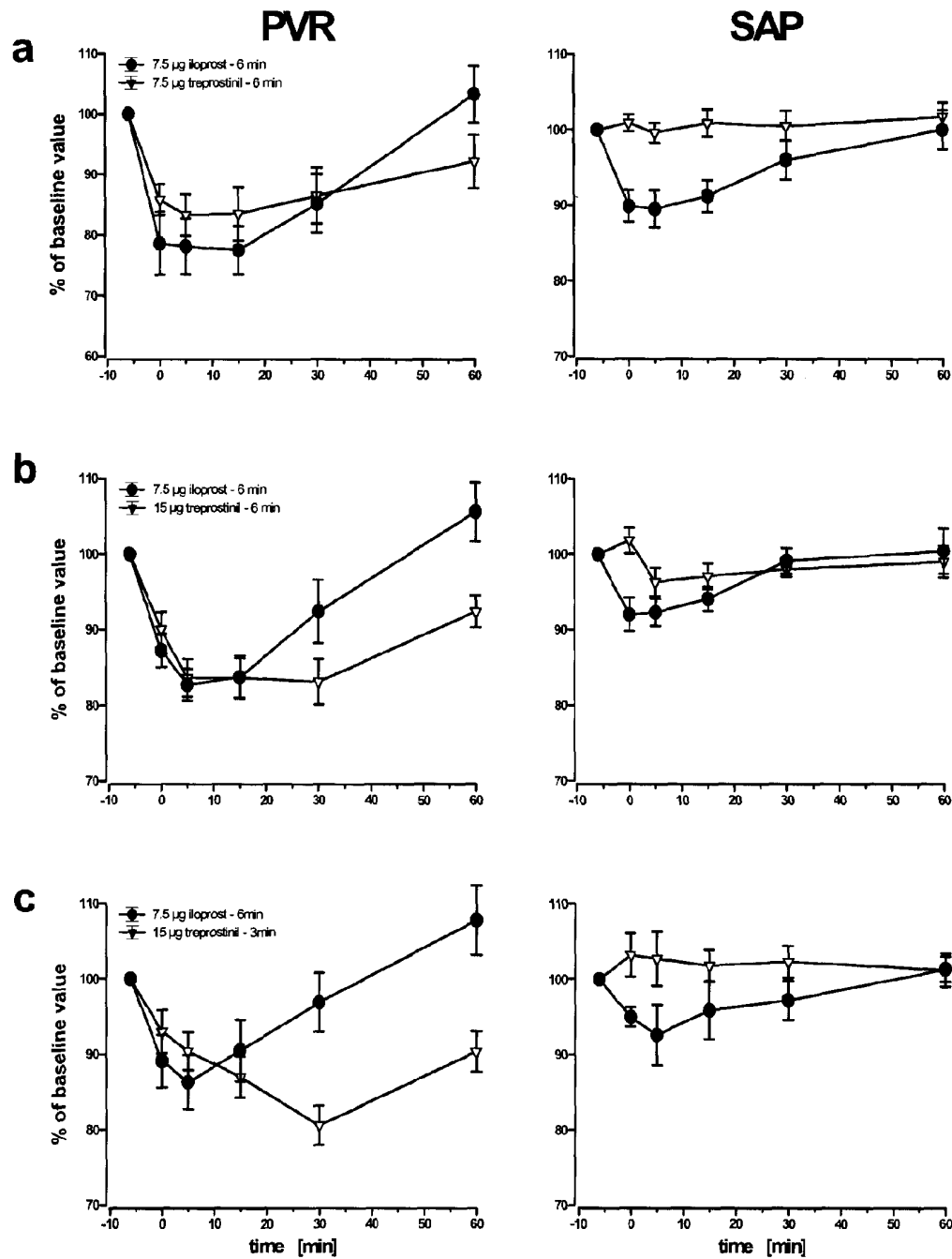


FIGURE 6



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FIGURE 7

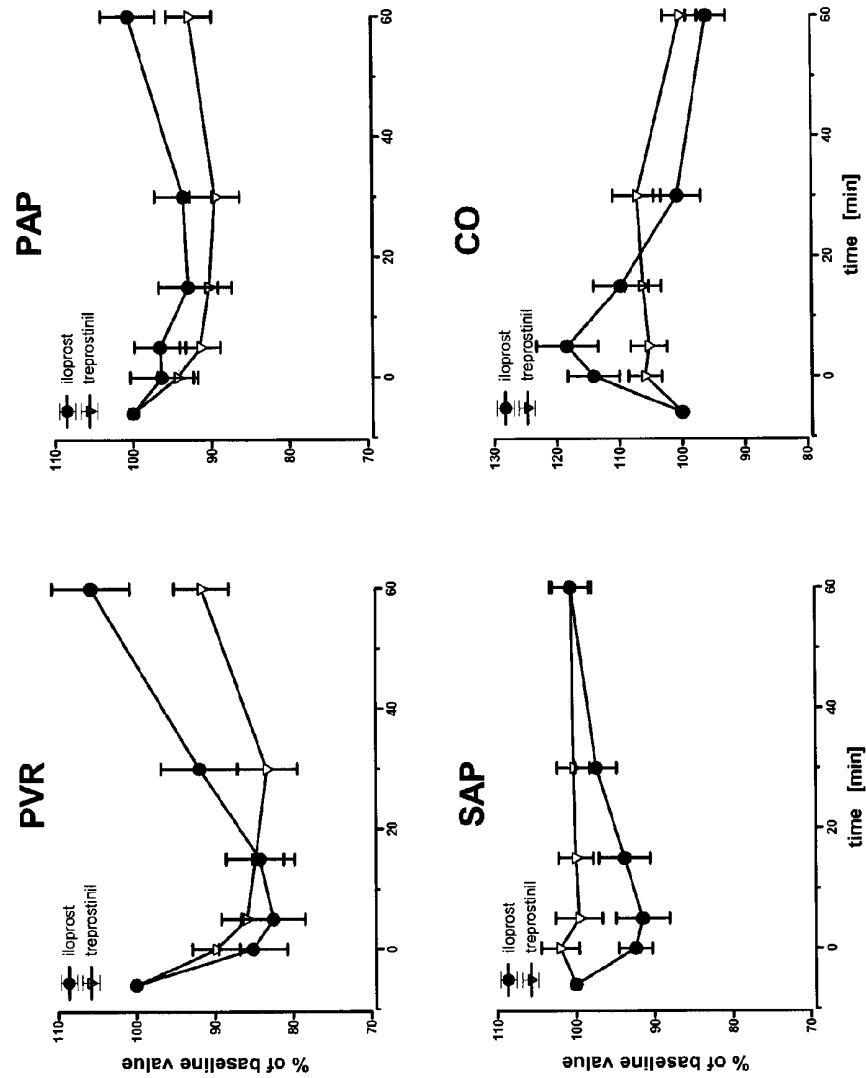


FIGURE 8

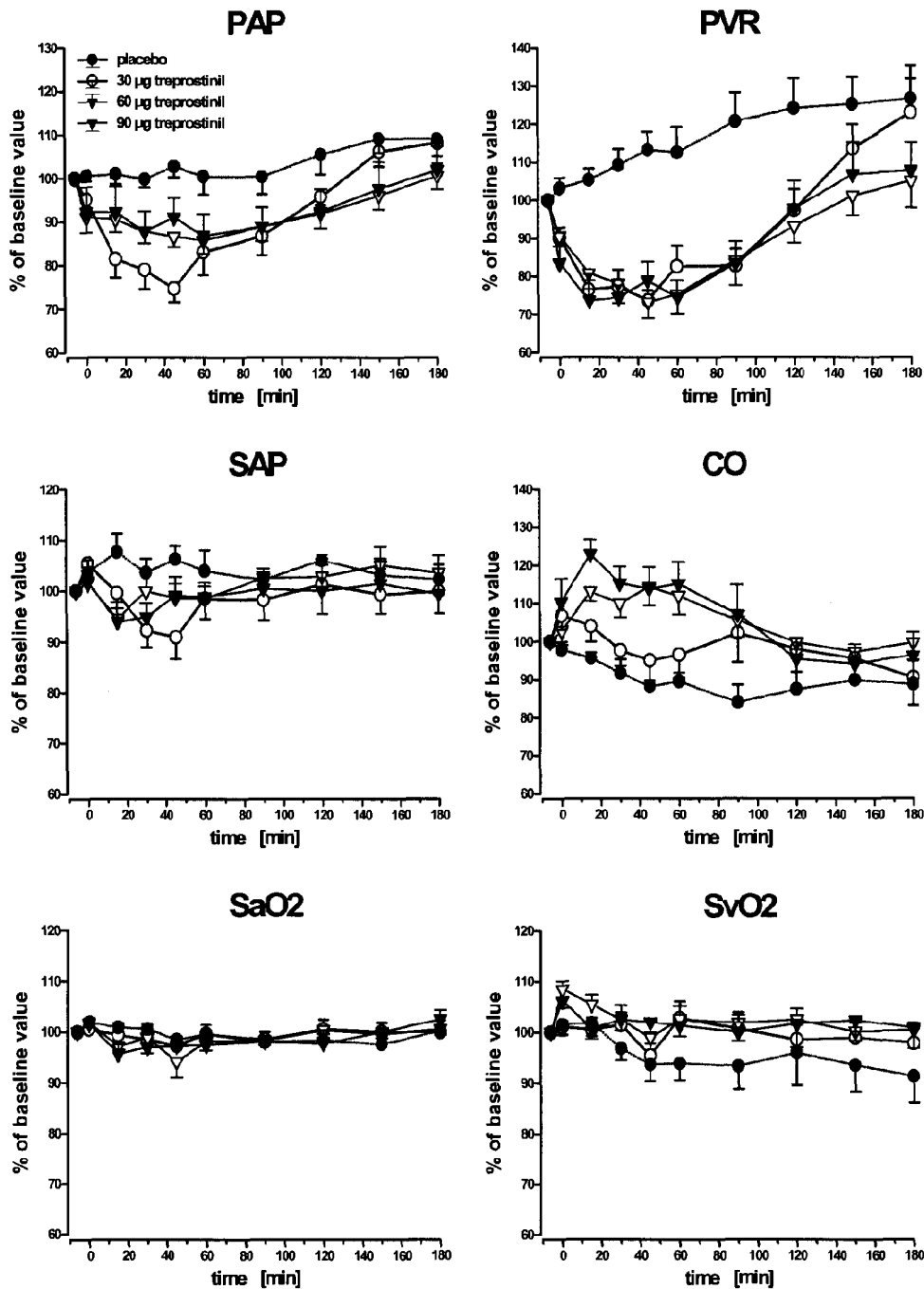
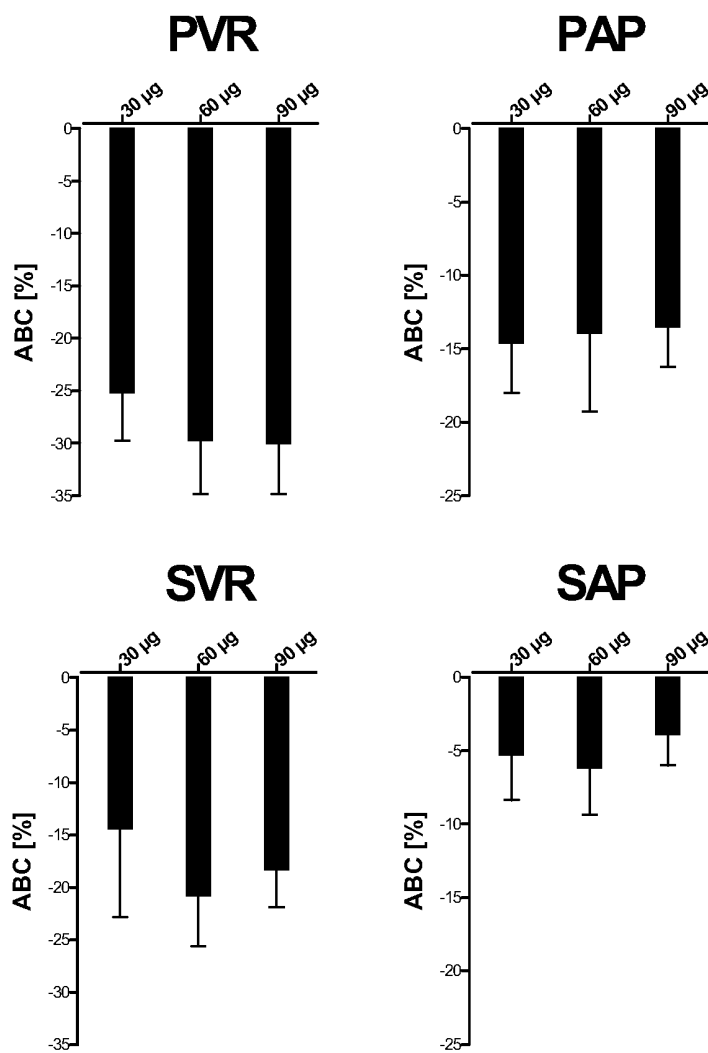


FIGURE 9



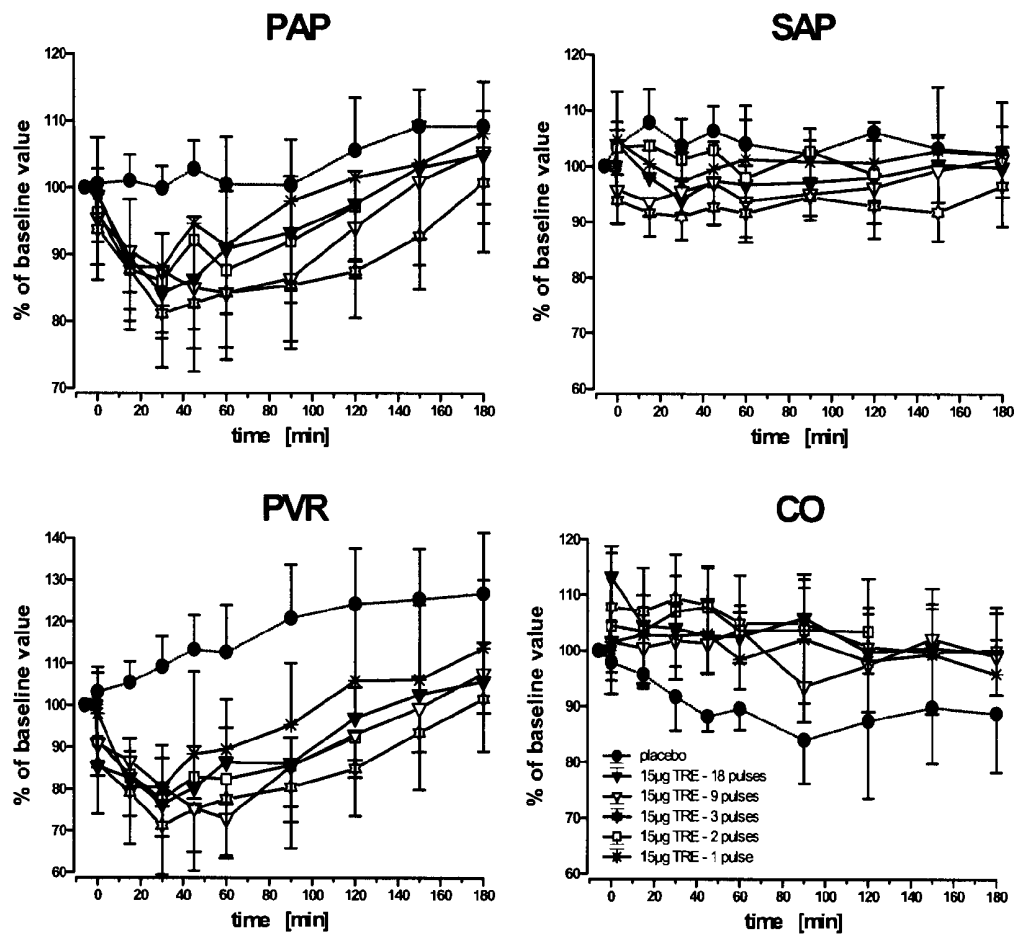
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FIGURE 10



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FIGURE 11

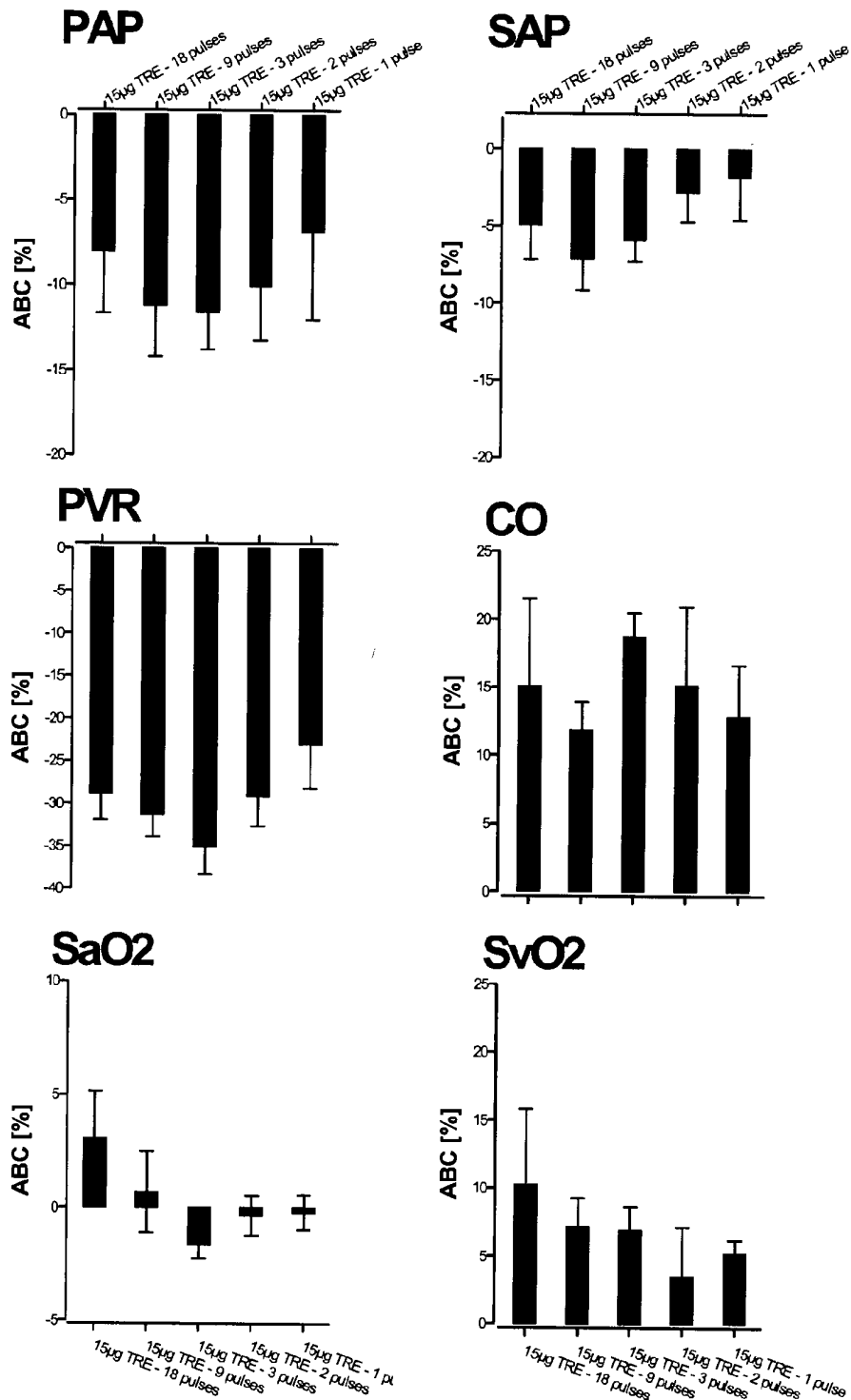
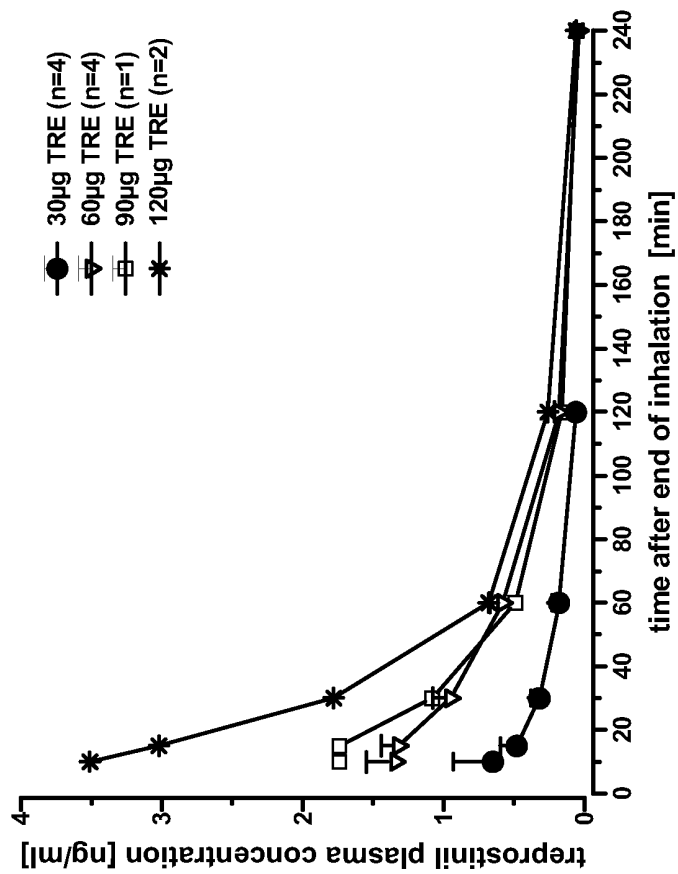


FIGURE 12



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TREPROSTINIL ADMINISTRATION BY INHALATION

CROSS REFERENCE TO RELATED APPLICATIONS

The present application is a Divisional of U.S. application Ser. No. 12/591,200, filed Nov. 12, 2009, which is a Continuation of U.S. application Ser. No. 11/748,205, filed May 14, 2007, which claims priority to U.S. provisional application No. 60/800,016 filed May 15, 2006, which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

The present application relates to methods and kits for therapeutic treatment and, more particularly, to therapeutic methods involving administering treprostinil using a metered dose inhaler and related kits.

BACKGROUND OF THE INVENTION

All blood is driven through the lungs via the pulmonary circulation in order, among other things, to replenish the oxygen which it dispenses in its passage around the rest of the body via the systemic circulation. The flow through both circulations is in normal circumstances equal, but the resistance offered to it in the pulmonary circulation is generally much less than that of the systemic circulation. When the resistance to pulmonary blood flow increases, the pressure in the circulation is greater for any particular flow. The above described condition is referred to as pulmonary hypertension (PH). Generally, pulmonary hypertension is defined through observations of pressures above the normal range pertaining in the majority of people residing at the same altitude and engaged in similar activities.

Pulmonary hypertension may occur due to various reasons and the different entities of pulmonary hypertension were classified based on clinical and pathological grounds in 5 categories according to the latest WHO convention, see e.g. Simonneau G., et al. J. Am. Coll. Cardiol. 2004; 43(12 Suppl S):5S-12S. Pulmonary hypertension can be a manifestation of an obvious or explicable increase in resistance, such as obstruction to blood flow by pulmonary emboli, malfunction of the heart's valves or muscle in handling blood after its passage through the lungs, diminution in pulmonary vessel caliber as a reflex response to alveolar hypoxia due to lung diseases or high altitude, or a mismatch of vascular capacity and essential blood flow, such as shunting of blood in congenital abnormalities or surgical removal of lung tissue. In addition, certain infectious diseases, such as HIV and liver diseases with portal hypertension may cause pulmonary hypertension. Autoimmune disorders, such as collagen vascular diseases, also often lead to pulmonary vascular narrowing and contribute to a significant number of pulmonary hypertension patients. The cases of pulmonary hypertension remain where the cause of the increased resistance is as yet inexplicable are defined as idiopathic (primary) pulmonary hypertension (iPAH) and are diagnosed by and after exclusion of the causes of secondary pulmonary hypertension and are in the majority of cases related to a genetic mutation in the bone morphogenetic protein receptor-2 gene. The cases of idiopathic pulmonary arterial hypertension tend to comprise a recognizable entity of about 40% of patients cared for in large specialized pulmonary hypertension centers. Approximately 65% of the most commonly afflicted are female and young adults, though it has occurred in children and patients over 50.

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Life expectancy from the time of diagnosis is short without specific treatment, about 3 to 5 years, though occasional reports of spontaneous remission and longer survival are to be expected given the nature of the diagnostic process. Generally, however, disease progress is inexorable via syncope and right heart failure and death is quite often sudden.

Pulmonary hypertension refers to a condition associated with an elevation of pulmonary arterial pressure (PAP) over normal levels. In humans, a typical mean PAP is approximately 12-15 mm Hg. Pulmonary hypertension, on the other hand, can be defined as mean PAP above 25 mmHg, assessed by right heart catheter measurement. Pulmonary arterial pressure may reach systemic pressure levels or even exceed these in severe forms of pulmonary hypertension. When the PAP markedly increases due to pulmonary venous congestion, i.e. in left heart failure or valve dysfunction, plasma can escape from the capillaries into the lung interstitium and alveoli. Fluid buildup in the lung (pulmonary edema) can result, with an associated decrease in lung function that can in some cases be fatal. Pulmonary edema, however, is not a feature of even severe pulmonary hypertension due to pulmonary vascular changes in all other entities of this disease.

Pulmonary hypertension may either be acute or chronic. Acute pulmonary hypertension is often a potentially reversible phenomenon generally attributable to constriction of the smooth muscle of the pulmonary blood vessels, which may be triggered by such conditions as hypoxia (as in high-altitude sickness), acidosis, inflammation, or pulmonary embolism. Chronic pulmonary hypertension is characterized by major structural changes in the pulmonary vasculature, which result in a decreased cross-sectional area of the pulmonary blood vessels. This may be caused by, for example, chronic hypoxia, thromboembolism, collagen vascular diseases, pulmonary hypercirculation due to left-to-right shunt, HIV infection, portal hypertension or a combination of genetic mutation and unknown causes as in idiopathic pulmonary arterial hypertension.

Pulmonary hypertension has been implicated in several life-threatening clinical conditions, such as adult respiratory distress syndrome ("ARDS") and persistent pulmonary hypertension of the newborn ("PPHN"). Zapol et al., Acute Respiratory Failure, p. 241-273, Marcel Dekker, New York (1985); Peckham, J. Ped. 93:1005 (1978). PPHN, a disorder that primarily affects full-term infants, is characterized by elevated pulmonary vascular resistance, pulmonary arterial hypertension, and right-to-left shunting of blood through the patent ductus arteriosus and foramen ovale of the newborn's heart. Mortality rates range from 12-50%. Fox, Pediatrics 59:205 (1977); Dworetz, Pediatrics 84: 1(1989). Pulmonary hypertension may also ultimately result in a potentially fatal heart condition known as "cor pulmonale," or pulmonary heart disease. Fishman, "Pulmonary Diseases and Disorders" 2nd Ed., McGraw-Hill, New York (1988).

Currently, there is no treatment for pulmonary hypertension that can be administered using a compact inhalation device, such as a metered dose inhaler.

SUMMARY OF THE INVENTION

One embodiment is a method of delivering to a subject in need thereof a therapeutically effective amount of treprostinil, or treprostinil derivative or a pharmaceutically acceptable salt thereof comprising administering to the subject a therapeutically effective amount of the treprostinil or treprostinil derivative or a pharmaceutically acceptable salt thereof using a metered dose inhaler.

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Another embodiment is a method for treating pulmonary hypertension comprising administering to a subject in need thereof treprostinil or its derivative, or a pharmaceutically acceptable salt thereof using a metered dose inhaler.

Yet another embodiment is a kit comprising a metered dose inhaler containing a pharmaceutical formulation comprising treprostinil or treprostinil derivative, or a pharmaceutically acceptable salt thereof.

And yet another embodiment is a kit for treating pulmonary hypertension in a subject, comprising (i) an effective amount of treprostinil or its derivative, or a pharmaceutically acceptable salt thereof; (ii) a metered dose inhaler; (iii) instructions for use in treating pulmonary hypertension.

Administration of treprostinil using a metered dose inhaler can provide patients, such as pulmonary hypertension patients, with a high degree of autonomy.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 pulmonary and systemic changes in hemodynamics following the inhalation of placebo (open circles), 30 μ g treprostinil (triangles), 45 μ g treprostinil (squares) or 60 μ g TREprostinil (black circles) applied by a Metered Dose Inhaler (MDI-TRE). A single short inhalation of treprostinil induced sustained reduction of PAP and PVR that outlasted the observation period of 120 minutes at doses of 45 and 60 μ g MDI-TRE. Systemic arterial pressure and resistance were not significantly affected. PAP=mean pulmonary artery pressure; PVR=pulmonary vascular resistance; SAP=mean systemic arterial pressure; SVR=systemic vascular resistance. Data are given as mean value \pm standard error of the mean (SEM).

FIG. 2 presents hemodynamic changes induced by the inhalation of placebo (open circles), 30 μ g treprostinil (triangles), 45 μ g treprostinil (squares) or 60 μ g treprostinil (black circles) applied by a metered dose inhaler. Treprostinil induced sustained elevation of cardiac output. Heart rate was rather unchanged as a sign for low spillover of MDI-TRE to the systemic circulation. Gas exchange was not negatively affected. CO=cardiac output; HR=heart rate; SaO₂=arterial oxygen saturation; SvO₂=central venous oxygen saturation. Data are given as mean value \pm SEM.

FIG. 3 shows areas under the curve for changes in pulmonary vascular resistance (PVR) calculated for an observation period of 120 minutes after inhalation treprostinil using a metered dose inhaler. PVR was markedly lowered by treprostinil inhalation. The increased pulmonary vasodilation over time with the two highest doses mainly relies on the more sustained effect over time. Data are shown as mean value \pm 95% confidence intervals.

FIG. 4 demonstrates Ventilation-perfusion matching measured with the multiple inert gas elimination technique. Five patients (30 μ g TRE, n=2; 45 μ g TRE, n=1; 60 μ g TRE, n=2) with pre-existing gas exchange problems were investigated for changes in ventilation-perfusion ratios. All patients had significant shunt flow at baseline. Shunt-flow and low V/Q areas were not significantly changed by nitric oxide (NO) inhalation or treprostinil inhalation using a metered dose inhaler (MDI-TRE). MDI-TRE applied at high treprostinil concentrations did not negatively affect ventilation-perfusion matching and gas-exchange. Data are given as mean value \pm 95% confidence intervals.

FIG. 5 presents response of pulmonary vascular resistance (PVR) to inhaled treprostinil vs. iloprost—period effects. a) First inhalation with treprostinil (n=22) vs. first inhalation with iloprost (n=22); b) second inhalation with treprostinil (n=22) vs. second inhalation with iloprost (n=22). The PVR decrease with treprostinil was delayed and prolonged, com-

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pared to iloprost. Due to carryover effects from the first period, in the second period, the effects of both drugs appeared shortened. Data are shown as percent of baseline values (mean value \pm 95% confidence interval).

FIG. 6 presents response of PVR and systemic arterial pressure (SAP) to inhalation of treprostinil vs. iloprost—dose effects. a) Inhalation of 7.5 μ g iloprost (in 6 min) vs. 7.5 μ g treprostinil (6 min) (n=14, in a randomized order). b) Inhalation of 7.5 μ g iloprost (6 min) vs. 15 μ g treprostinil (6 min) (n=14, in randomized order). c) Inhalation of 7.5 μ g iloprost (6 min) vs. 15 μ g treprostinil (3 min) (n=16, in randomized order). Data are shown as percent of baseline values (mean \pm 95% confidence interval). Iloprost, filled circles; Treprostinil, open triangles.

FIG. 7 presents hemodynamic response to inhalation of treprostinil vs. iloprost. Data from n=44 patients, who inhaled both drugs in randomized order, shown as percent of baseline values (mean value \pm 95% confidence interval). PVR, pulmonary vascular resistance; PAP, mean pulmonary arterial pressure; SAP, mean systemic arterial pressure; CO, cardiac output.

FIG. 8 presents pharmacodynamics after treprostinil inhalation vs. placebo. Placebo or treprostinil in doses of 30 μ g, 60 μ g or 90 μ g were inhaled (means \pm 95% confidence intervals). Maximal decrease of PVR was comparable for all doses. The duration of pulmonary vasodilation (PVR-decrease) appeared to be dose dependent. PVR, pulmonary vascular resistance; PAP, mean pulmonary arterial pressure; SAP, mean systemic arterial pressure; CO, cardiac output; SaO₂, arterial oxygen saturation; SvO₂, mixed venous oxygen saturation.

FIG. 9 presents Areas Between the placebo and the treprostinil Curves (ABC). ABCs were calculated for a 3-hour period after inhalation of TRE or placebo from the relative changes of hemodynamic parameters (means \pm 95% confidence intervals). PVR, pulmonary vascular resistance; PAP, mean pulmonary arterial pressure; SAP, mean systemic arterial pressure; SVR, systemic vascular resistance.

FIG. 10 presents hemodynamic responses to the inhalation of 15 μ g treprostinil. The inhalation time by increasing treprostinil concentration. A pulse of aerosol was generated every 6 seconds. TRE aerosol was inhaled in concentrations of 100 μ g/ml (18 pulses; n=6), 200 μ g/ml (9 pulses; n=6), 600 μ g/ml (3 pulses; n=21), 1000 μ g/ml (2 pulses; n=7) and 2000 μ g/ml (1 pulse; n=8). Placebo data correspond to FIG. 8. Data are shown as means \pm 95% confidence intervals. PVR, pulmonary vascular resistance; PAP, mean pulmonary arterial pressure; SAP, mean systemic arterial pressure; CO, cardiac output.

FIG. 11 presents areas between the placebo curve and the responses to 15 μ g treprostinil applied at increasing concentrations to minimize inhalation time. Mean \pm SEM of relative changes of hemodynamic parameters (observation time 120 min). PAP, pulmonary arterial pressure, SAP, systemic arterial pressure, PVR, pulmonary vascular resistance, CO, cardiac output, SaO₂, systemic arterial oxygen saturation, SvO₂, pulmonary arterial oxygen saturation.

FIG. 12 presents pharmacokinetics of treprostinil after a single inhalation. Treprostinil plasma levels after inhalation of 30 μ g, 60 μ g, 90 μ g or 120 μ g treprostinil (6 min inhalation period; experiments correspond to those shown in FIGS. 8 and 9). Data with error bars represent mean values \pm SEM.

DETAILED DESCRIPTION OF THE INVENTION

Unless otherwise specified, the term “a” or “an” used herein shall mean “one or more.”

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The present application incorporates herein by reference in its entirety Voswinckel R, et al. J. Am. Coll. Cardiol. 2006; 48:1672-1681.

The inventors discovered that a therapeutically effective dose of treprostinil can be administered in a few single inhalations using a compact inhalation device, such as a metered dose inhaler. Furthermore, the inventors discovered that such administering does not cause significant side effects, especially no significant side effects related to systemic blood pressure and circulation as well as no gas exchange deteriorations or disruptions.

Accordingly, one embodiment of the invention is a method of delivering to a subject in need thereof, such as a human being, a therapeutically effective amount of treprostinil comprising administering to the subject a formulation comprising a therapeutically effective amount of treprostinil, its derivative or a pharmaceutically acceptable salt thereof using a metered dose inhaler. Treprostinil can be administered via a metered dose inhaler to a subject affected with a condition or disease, which can be treated by treprostinil, such as asthma, pulmonary hypertension, peripheral vascular disease or pulmonary fibrosis.

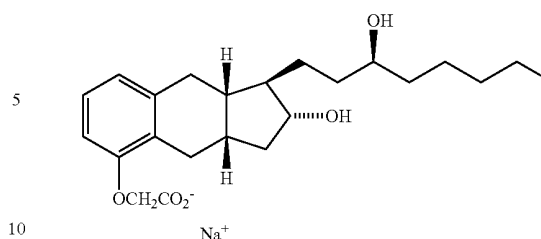
Another embodiment of the invention is a method for treating pulmonary hypertension, comprising administering to a subject in need thereof, such as a human being, treprostinil or its derivative, or a pharmaceutically acceptable salt using a metered dose inhaler.

Treprostinil, or 9-deoxy-2',9- α -methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)-13,14-dihydro-prostaglandin F₁, is a prostacyclin analogue, first described in U.S. Pat. No. 4,306,075. U.S. Pat. No. 5,153,222 describes use of treprostinil for treatment of pulmonary hypertension. Treprostinil is approved for the intravenous as well as subcutaneous route, the latter avoiding septic events associated with continuous intravenous catheters. U.S. Pat. Nos. 6,521,212 and 6,756,033 describe administration of treprostinil by inhalation for treatment of pulmonary hypertension, peripheral vascular disease and other diseases and conditions. U.S. Pat. No. 6,803,386 discloses administration of treprostinil for treating cancer such as lung, liver, brain, pancreatic, kidney, prostate, breast, colon and head-neck cancer. US patent application publication No. 2005/0165111 discloses treprostinil treatment of ischemic lesions. U.S. Pat. No. 7,199,157 discloses that treprostinil treatment improves kidney functions. US patent application publication No. 2005/0282903 discloses treprostinil treatment of neuropathic foot ulcers. U.S. provisional application No. 60/900,320 filed Feb. 9, 2007, discloses treprostinil treatment of pulmonary fibrosis.

The term "acid derivative" is used herein to describe C1-4 alkyl esters and amides, including amides wherein the nitrogen is optionally substituted by one or two C1-4 alkyl groups.

The present invention also encompasses methods of using Treprostinil or its derivatives, or pharmaceutically acceptable salts thereof. In one embodiment, a method uses Treprostinil sodium, currently marketed under the trade name of REMODULIN®. The FDA has approved Treprostinil sodium for the treatment of pulmonary arterial hypertension by injection of dose concentrations of 1.0 mg/mL, 2.5 mg/mL, 5.0 mg/mL and 10.0 mg/mL. The chemical structure formula for Treprostinil sodium is:

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Treprostinil sodium is sometimes designated by the chemical names: (a) [(1R,2R,3aS,9aS)-2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[*f*]inden-5-yl]oxy]acetic acid; or (b) 9-deoxy-2',9- α -methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)-13,14-dihydro-prostaglandin F₁. Treprostinil sodium is also known as: UT-15; LRX-15; 15AU81; UNIPROST™; BW A15AU; and U-62,840. The molecular weight of Treprostinil sodium is 390.52, and its empirical formula is C₂₃H₃₄O₅.

In certain embodiments, treprostinil can be administered in combination with one or more additional active agents. In some embodiments, such one or more additional active agents can be also administered together with treprostinil using a metered dose inhaler. Yet in some embodiments, such one or more additional active agents can be administered separately from treprostinil. Particular additional active agents that can be administered in combination with treprostinil may depend on a particular disease or condition for treatment or prevention of which treprostinil is administered. In some cases, the additional active agent can be a cardiovascular agent such as a calcium channel blocker, a phosphodiesterase inhibitor, an endothelial antagonist, or an antiplatelet agent.

The present invention extends to methods of using physiologically acceptable salts of Treprostinil, as well as non-physiologically acceptable salts of Treprostinil that may be used in the preparation of the pharmacologically active compounds of the invention.

The term "pharmaceutically acceptable salt" refers to a salt of Treprostinil with an inorganic base, organic base, inorganic acid, organic acid, or basic or acidic amino acid. Salts of inorganic bases can be, for example, salts of alkali metals such as sodium or potassium; alkaline earth metals such as calcium and magnesium or aluminum; and ammonia. Salts of organic bases can be, for example, salts trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, and triethanolamine. Salts of inorganic acids can be, for example, salts of hydrochloric acid, hydroboric acid, nitric acid, sulfuric acid, and phosphoric acid. Salts of organic acids can be, for example, salts of formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, lactic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, and p-toluenesulfonic acid. Salts of basic amino acids can be, for example, salts of arginine, lysine and ornithine. Salts of acidic amino acids can include, for example, salts of aspartic acid and glutamic acid. Quaternary ammonium salts can be formed, for example, by reaction with lower alkyl halides, such as methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides, with dialkyl sulphates, with long chain halides, such as decyl, lauryl, myristyl, and stearyl chlorides, bromides, and iodides, and with aralkyl halides, such as benzyl and phenethyl bromides.

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Preferred pharmaceutically acceptable salts are disclosed, for example, in US patent application publication No. 20050085540.

Treprostinil can be administered by inhalation, which in the present context refers to the delivery of the active ingredient or a combination of active ingredients through a respiratory passage, wherein the subject in need of the active ingredient(s) through the subject's airways, such as the subject's nose or mouth.

A metered dose inhaler in the present context means a device capable of delivering a metered or bolus dose of respiratory drug, such as treprostinil, to the lungs. One example of the inhalation device can be a pressurized metered dose inhaler, a device which produces the aerosol clouds for inhalation from solutions and/or suspensions of respiratory drugs in chlorofluorocarbon (CFC) and/or hydrofluoroalkane (HFA) solutions.

The inhalation device can be also a dry powder inhaler. In such case, the respiratory drug is inhaled in solid formulation, usually in the form of a powder with particle size less than 10 micrometers in diameter or less than 5 micrometers in diameter.

The metered dose inhaler can be a soft mist inhaler (SMI), in which the aerosol cloud containing a respiratory drug can be generated by passing a solution containing the respiratory drug through a nozzle or series of nozzles. The aerosol generation can be achieved in SMI, for example, by mechanical, electromechanical or thermomechanical process. Examples of soft mist inhalers include the Respimat® Inhaler (Boeinger Ingelheim GmbH), the AERx® Inhaler (Aradigm Corp.), the Mystic™ Inhaler (Ventaira Pharmaceuticals, Inc) and the Aira™ Inhaler (Chrysalis Technologies Incorporated). For a review of soft mist inhaler technology, see e.g. M. Hindle, The Drug Delivery Companies Report, Autumn/Winter 2004, pp. 31-34. The aerosol for SMI can be generated from a solution of the respiratory drug further containing pharmaceutically acceptable excipients. In the present case, the respiratory drug is treprostinil, its derivative or a pharmaceutically acceptable salt thereof, which can be formulated in SMI as a solution. The solution can be, for example, a solution of treprostinil in water, ethanol or a mixture thereof. Preferably, the diameter of the treprostinil-containing aerosol particles is less than about 10 microns, or less than about 5 microns, or less than about 4 microns.

Treprostinil concentration in an aerosolable formulation, such as a solution, used in a metered dose inhaler can range from about 500 µg/ml to about 2500 µg/ml, or from about 800 µg/ml to about 2200 µg/ml, or from about 1000 µg/ml to about 2000 µg/ml.

The dose of treprostinil that can be administered using a metered dose inhaler in a single event can be from about 15 µg to about 100 µg or from about 15 µg to about 90 µg or from about 30 µg to about 90 µg or from about 30 µg to about 60 µg.

Administering of treprostinil in a single event can be carried out in a limited number of breaths by a patient. For example, treprostinil can be administered in 20 breaths or less, or in 10 breaths or less, or than 5 breaths or less. Preferably, treprostinil is administered in 3, 2 or 1 breaths.

The total time of a single administering event can be less than 5 minutes, or less than 1 minute, or less than 30 seconds.

Treprostinil can be administered a single time per day or several times per day.

In some embodiments, the method of treatment of pulmonary hypertension can further comprise administering at least one supplementary agent selected from the group consisting of sildenafil, tadalafil, calcium channel blockers (diltiazem, amlodipine, nifedipine), bosentan, sitaxsentan, ambrisentan,

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and pharmaceutically acceptable salts thereof. In some embodiments, the supplementary agents can be included in the treprostinil formulation and, thus, can be administered simultaneously with treprostinil using a metered dose inhaler. In some embodiments, the supplementary agents can be administered separately from treprostinil. In some embodiments, the application of intravenous prostacyclin (flolan), intravenous iloprost or intravenous or subcutaneous treprostinil can be administered in addition to treprostinil administered via inhalation using a metered dose inhaler.

The present invention also provides a kit that includes a metered dose inhaler containing a pharmaceutical formulation comprising treprostinil or its derivative, or a pharmaceutically acceptable salt thereof. Such a kit can further include instructions on how to use the metered dose inhaler for inhaling treprostinil. Such instructions can include, for example, information on how to coordinate patient's breathing, and actuation of the inhaler. The kit can be used by a subject, such as human being, affected with a disease or condition that can be treated by treprostinil, such as asthma, pulmonary hypertension, peripheral vascular disease or pulmonary fibrosis.

In some cases, the kit is a kit for treating pulmonary hypertension, that includes (i) a metered dose inhaler containing a pharmaceutical formulation comprising treprostinil or its derivative, or a pharmaceutically acceptable salt thereof; and (ii) instructions for use of the metered dose inhaler containing treprostinil in treating pulmonary hypertension.

As used herein, the phrase "instructions for use" shall mean any FDA-mandated labeling, instructions, or package inserts that relate to the administration of Treprostinil or its derivatives, or pharmaceutically acceptable salts thereof, for treatment of pulmonary hypertension by inhalation. For example, instructions for use may include, but are not limited to, indications for pulmonary hypertension, identification of specific symptoms associated with pulmonary hypertension, that can be ameliorated by Treprostinil, recommended dosage amounts for subjects suffering from pulmonary hypertension and instructions on coordination of individual's breathing and actuation of the metered dose inhaler.

The present invention can be illustrated in more detail by the following example, however, it should be understood that the present invention is not limited thereto.

EXAMPLE 1

Open Label Study Upon Acute Safety, Tolerability and Hemodynamic Effects of Inhaled Treprostinil Delivered in Seconds

A study was conducted of acute vasodilator challenge during right heart catheter investigation to determine the safety, tolerability and pulmonary vasodilatory potency of inhaled treprostinil applied in seconds by a soft mist inhaler (SMI-TRE). The study produced evidence for a long lasting favourable effect of SMI-TRE on pulmonary hemodynamics in absence of systemic side effects and gas exchange disruptions.

Summary:

Inhaled nitric oxide (20 ppm; n=45) and inhaled treprostinil sodium (TRE; n=41) or placebo (n=4) were applied once during right heart catheter investigation. TRE was delivered in 2 breaths (1000 µg/ml aerosol concentration; 30 µg dose; n=12), 3 breaths (1000 µg/ml; 45 µg; n=9) or 2 breaths (2000 µg/ml; 60 µg; n=20) from a Respimat® SMI. Pulmonary hemodynamics and blood gases were measured at defined time points, observation time following TRE application was 120 minutes. TRE doses of 30 µg, 45 µg and 60 µg reduced

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pulmonary vascular resistance (PVR) to $84.4 \pm 8.7\%$, $71.4 \pm 17.5\%$ and $77.5 \pm 7.2\%$ of baseline values, respectively (mean $\pm 95\%$ confidence interval). The 120 minute area under the curve for PVR for placebo, 30 μg , 45 μg and 60 μg TRE was 1230 ± 1310 , -870 ± 940 , -2450 ± 2070 and -2000 ± 900 min %, respectively. Reduction of PVR by a single inhalation of the two higher doses outlasted the observation period of 120 minutes. Reduction of systemic vascular resistance and pressure was negligible, showing a high pulmonary selectivity for SMI-TRE. Intrapulmonary selectivity was also provided by SMI-TRE as ventilation/perfusion matching, assessed by the multiple inert gas elimination technique in 5 patients with gas exchange problems, was not significantly different after SMI-TRE compared to inhaled nitric oxide or no treatment. No significant side effects were observed.

Conclusions: The acute application of inhaled treprostinil with a metered dose inhaler in 2-3 breaths was safe, well tolerated and induced a strong and sustained pulmonary selective vasodilation.

Methods and Patients

A total number of 45 patients with moderate to severe precapillary pulmonary hypertension were enrolled. Patient characteristics were: female to male ratio (f/m)=29/16, age 59 ± 2.3 years, pulmonary artery pressure (PAP) 45 ± 1.8 mmHg, pulmonary vascular resistance (PVR) 743 ± 52 dynes·s·cm⁻⁵, pulmonary artery wedge pressure (PAWP) 8.6 ± 0.5 mmHg, central venous pressure (CVP) 6.4 ± 0.7 mmHg, cardiac output (CO) 4.5 ± 0.2 l/min, central venous oxygen saturation (SvO₂) 62.3 ± 1.2 mmHg (mean \pm Standard Error of the Mean). Disease etiologies were idiopathic PAH (iPAH) (n=13), PAH other (n=11), chronic thromboembolic pulmonary hypertension (CTEPH) (n=17) and pulmonary fibrosis (n=4). Table 1 presents the patient characteristics of the different groups.

TABLE 1

Patient characteristics of the different treatment groups.				
	Placebo (n = 4)	30 μg TRE (n = 12)	45 μg TRE (n = 9)	60 μg TRE (n = 20)
Age [years]	61 \pm 8	53.9 \pm 3.9	54.2 \pm 5.7	65.5 \pm 3.1
PAP [mmHg]	49.5 \pm 10.1	45 \pm 3.1	54.3 \pm 2.8	39.7 \pm 2.0
PVR [Dynes]	896 \pm 163	597 \pm 53.9	1049 \pm 107	663 \pm 81
CO [l/min]	4.46 \pm 0.9	5.2 \pm 0.4	3.9 \pm 0.4	4.4 \pm 0.3
SAP [mmHg]	98 \pm 8.1	90.1 \pm 3.2	82.8 \pm 3.9	86.1 \pm 2.0
SaO ₂ [%]	85.3 \pm 4.5	90.0 \pm 1.1	89.6 \pm 1.1	90.6 \pm 0.5
SvO ₂ [%]	57.5 \pm 3.9	66.0 \pm 1.6	59.1 \pm 3.4	62.5 \pm 1.6

Data are given as mean \pm Standard Error of the Mean (SEM).

PAP = pulmonary artery pressure;

PVR = pulmonary vascular resistance;

CO = cardiac output;

SAP = systemic arterial pressure;

SaO₂ = arterial oxygen saturation;

SvO₂ = central venous oxygen saturation.

Baseline values were determined 20-30 minutes after placement of the catheter. Heart rate, pulmonary and systemic blood pressure and cardiac output were measured and blood gases were taken during each pharmacological intervention at defined time points. Pharmacological interventions included the inhalation of 20 ppm nitric oxide (NO) after evaluation of baseline parameters (n=45) and the consecutive inhalation of placebo (n=4), 30 μg SMI-TRE (n=12), 45 μg SMI-TRE (n=9) or 60 μg (n=20) SMI-TRE. Placebo and treprostinil was applied with the Respimat® SMI. For filling of this device with treprostinil sodium, the placebo solution was withdrawn from the device with a syringe and treprostinil solution was injected into the device under sterile conditions. Aerosol

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quality was controlled before and after refilling of the SMI devices by laser diffractometry, see e.g. Gessler T., Schmehl T., Hoepfer M. M., Rose F., Ghofrani H. A., Olschewski H. et al. Ultrasonic versus jet nebulization of iloprost in severe pulmonary hypertension. Eur. Respir. J. 2001; 17:14-19 incorporated herein in its entirety. The aerosol sizes before (placebo) and after filling (treprostinil) were unchanged. The aerosol particles mass median aerodynamic diameter of treprostinil-aerosol was 4-5 μm , which can be at the upper limit for alveolar deposition. The aerosol volume delivered by one cycle from the SMI was 15 μl . The solution used for aerosol generation was prepared from treprostinil sodium salt using a standard protocol. The SMI was either filled with a concentration of 1000 $\mu\text{g}/\text{ml}$ treprostinil sodium (one aerosol puff=15 μg TRE) or with 2000 $\mu\text{g}/\text{ml}$ (one puff=30 μg TRE). The different doses were applied as 2 puffs 1000 $\mu\text{g}/\text{ml}$ (30 μg), 3 puffs 1000 $\mu\text{g}/\text{ml}$ (45 μg) and 2 puffs 2000 $\mu\text{g}/\text{ml}$ (60 μg). The placebo was inhaled as 2 puffs from a placebo-SMI. Hemodynamics and gas-exchange parameters were recorded for 120 minutes after TRE inhalation. This study used the Respimat® device, because the implemented "soft mist" technology was well suited for the deposition of such highly active drugs like prostanoids.

The impact of SMI-TRE on ventilation-perfusion matching was assessed in five patients (30 μg TRE, n=2; 45 μg TRE, n=1; 60 μg TRE, n=2) with pre-existing gas exchange problems by use of the multiple inert gas elimination technique (MIGET), see e.g. Wagner P D, Saltzman H A, West J B. Measurement of continuous distributions of ventilation-perfusion ratios: theory. J Appl Physiol. 1974; 36:588-99; Ghofrani H A, Wiedemann R, Rose F, Schermuly R T, Olschewski H, Weissmann N et al. Sildenafil for treatment of lung fibrosis and pulmonary hypertension: a randomised controlled trial. Lancet. 2002; 360:895-900, both incorporated herein in their entirety.

Statistics:

Mean values, standard deviation, standard error of the mean and 95% confidence intervals were calculated. Statistical analysis was done by use of a paired t-test.

Results:

The inhalation of treprostinil sodium from the metered dose inhaler (SMI-TRE) was well tolerated, only mild and transient cough for a maximum of one minute was reported. No systemic side effects like headache, flush, nausea or dizziness were observed.

Two to three breaths of SMI-TRE induced a strong pulmonary vasodilation that outlasted the observation time of 120 minutes (45 and 60 μg). The lower dose of 30 μg TRE induced a somewhat shorter effect on pulmonary vascular resistance; however, the maximal pulmonary vasodilation was comparable. In contrast, placebo inhalation did not induce pulmonary vasodilation. In fact a slight increase in PVR over the time of the right heart catheter investigation could be recorded following placebo inhalation (FIG. 1). The effect of SMI-TRE on systemic vascular resistance and pressure was very small and not clinically significant. Cardiac output was significantly increased over the whole observation period, whereas heart rate was rather unchanged. Gas exchange was not influenced by SMI-TRE (FIG. 2). The maximal changes in hemodynamic and gas-exchange parameters compared to baseline values are depicted in Table 2.

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TABLE 2

Extremes of the relative changes of hemodynamic and gas exchange parameters compared to baseline after inhalation of Placebo (n = 4), 30 µg treprostinil (n = 12), 45 µg treprostinil (n = 9) and 60 µg treprostinil (n = 20). Highest (max) and lowest (min) values during the observation period are shown.

	Placebo	30 µg TRE	45 µg TRE	60 µg TRE
PAP (min)	99.4 ± 3.0	83.4 ± 3.2	77.6 ± 6.8	79.5 ± 2.4
PVR (min)	101.4 ± 1.9	84.4 ± 4.4	71.4 ± 8.9	77.5 ± 3.7
CO (max)	99.7 ± 1.1	108.8 ± 3.8	108.6 ± 5.6	103.8 ± 2.0
SVR (min)	104.3 ± 4.3	97.7 ± 4.2	92 ± 3.9	91.3 ± 2.1
SAP (min)	102.7 ± 1.7	97.3 ± 1.9	96.1 ± 1.5	93.6 ± 2.9
HR (max)	105 ± 2.1	106.1 ± 2.9	99.1 ± 2.4	101.1 ± 0.9
SaO ₂ (min)	98.2 ± 0.4	101 ± 0.3	94.4 ± 1.8	95.8 ± 0.9
SvO ₂ (max)	104.5 ± 1.4	102.4 ± 1.3	104.5 ± 4.4	102 ± 1.0

Data are given as percent of baseline values (mean ± SEM).

PAP = pulmonary artery pressure;

PVR = pulmonary vascular resistance;

SVR = systemic vascular resistance;

CO = cardiac output;

SAP = systemic arterial pressure;

HR = heart rate;

SaO₂ = arterial oxygen saturation;

SvO₂ = central venous oxygen saturation.

The areas under the curve for PVR were calculated for placebo and the different SMI-TRE doses over the 120 minute observation period (FIG. 3). A dose effect of SMI-TRE with a trend to a more sustained effect with the two highest doses could be observed.

The inhalation of a highly concentrated aerosol can be in theory prone to disturbances of gas exchange because the deposition of even small amounts of aerosol may deliver high doses locally and thereby antagonize the hypoxic pulmonary vasoconstriction in poorly ventilated areas. This would then lead to increased shunt flow or increase of low ventilation/perfusion (V/Q) areas. This question was addressed in five patients with the multiple inert gas elimination technique (MIGET), the gold-standard for intrapulmonary V/Q ratio determination. The MIGET patients were selected for pre-existing gas exchange limitations. Characteristics of these patients were: PAP 54.6±3.2 mmHg, PVR 892±88 dynes, SaO₂ 91.7±0.5%, SvO₂ 65.2±1.8%. Etiologies were iPAH (n=1), CTEPH (n=3), pulmonary fibrosis (n=1). The maximal relative reduction of SaO₂ after inhalation of SMI-TRE in these patients was -3.8±1.5% compared to baseline values. Shunt flow at baseline, NO-inhalation and 60 minutes after SMI-TRE was 6.4±4.3%, 5.4±3.0% and 8.3±3.4%, respectively (mean±95% confidence interval; FIG. 4).

No significant increase in low V/Q areas or shunt fraction after inhalation of SMI-TRE was observed, in fact the distribution of perfusion was not different to that at baseline and during nitric oxide inhalation. This proves an excellent intrapulmonary selectivity of SMI-TRE, which is also reflected by unchanged arterial oxygen saturation.

Conclusion:

Treprostinil is tolerated at high doses with no systemic side effects. The application of an effective amount of treprostinil in only few or even one single breath was achieved with a highly concentrated treprostinil sodium solution. Treprostinil can be applied by a metered dose inhaler, such as Respimat® soft mist inhaler.

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EXAMPLE 2

Investigation of the Effects of Inhaled Treprostinil on Pulmonary Hemodynamics and Gas Exchange in Severe Pulmonary Hypertension

This study investigated the effects of inhaled treprostinil on pulmonary vascular resistance in severe pulmonary hypertension and addressed systemic effects and gas exchange as well as tolerability and efficacy of high doses of treprostinil given in short time. A total of 123 patients with a mean pulmonary artery pressure of about 50 mmHg were investigated in three separate randomized studies. Inhaled treprostinil exerted potent sustained pulmonary vasodilation with excellent tolerability and could be safely applied in a few breaths or even one breath.

Summary:

Three different studies were conducted on a total of 123 patients by means of right heart catheterization: i) a randomized crossover-design study (44 patients), ii) a dose escalation study (31 patients) and iii) a study of reduction of inhalation time while keeping the dose fixed (48 patients). The primary endpoint was the change in pulmonary vascular resistance (PVR).

The mean pulmonary artery pressure of the enrolled patients was about 50 mmHg. Hemodynamics and patient characteristics were similar in all studies. In study i) TRE and Iloprost (ILO), at an inhaled dose of 7.5 µg, displayed comparable PVR decrease, with a significantly different time course (p<0.001), TRE exhibiting a more sustained effect on PVR (p<0.0001) and less systemic side effects. In study ii) placebo, 30 µg, 60 µg, 90 µg or 120 µg TRE were applied with drug effects being observed for 3 hours after inhalation. A near-maximal acute PVR decrease was observed at 30 µg TRE. In study iii) TRE was inhaled with a pulsed ultrasonic nebulizer, mimicking a metered dose inhaler. 15 µg TRE was inhaled with 18 pulses (TRE concentration 100 µg/ml), 9 pulses (200 µg/ml), 3 pulses (600 µg/ml), 2 pulses (1000 µg/ml) or 1 pulse (2000 µg/ml), each mode achieving comparable, sustained pulmonary vasodilation.

Inhaled treprostinil exerts sustained pulmonary vasodilation with excellent tolerability at doses, which may be inhaled in a few or even one breath. Inhaled treprostinil is advantageous to inhaled iloprost in terms of duration of effect and systemic side effects. Inhaled treprostinil is well tolerated in concentrations up to 2000 mg/ml (bringing down inhalation time to a single breath) and in high doses (up to 90 µg).

Methods:

All inhalations were performed with the OPTINEB® ultrasonic nebulizer (NebuteC, Elsenfeld, Germany).

Study i) was a randomized, open-label, single-blind crossover study. The primary objective was to compare the acute hemodynamic effects and the systemic side effects of inhaled treprostinil with inhaled iloprost at comparable doses. A total number of 44 patients with moderate to severe precapillary pulmonary hypertension were enrolled. Patient characteristics and hemodynamic as well as gas exchange parameters are outlined in Table 3.

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TABLE 3

Patient characteristics, hemodynamic parameters and gas exchange values at baseline, before challenge with inhalative prostanooids.												
	N	Age	Gender f/m	Etiology i/o/t/f	PAP [mmHg]	PVR [dyn*s*cm ⁻⁵]	SAP [mmHg]	CVP [mmHg]	PAWP [mmHg]	CO [l/min]	SaO ₂ [%]	SvO ₂ [%]
1a	14	55.1 ± 4.8	11/3	4/4/2/4	53.8 ± 3.1	911 ± 102	95.4 ± 3.6	7.4 ± 1	8.0 ± 0.8	4.3 ± 0.4	93.8 ± 2	63.9 ± 2.4
1b	14	54.1 ± 3.3	10/4	1/6/5/2	47.4 ± 3.8	716 ± 80	90.6 ± 3.3	5.9 ± 1.4	6.4 ± 0.7	4.7 ± 0.4	92 ± 1	64.4 ± 2.3
1c	16	56 ± 2.9	7/9	6/3/6/1	47.5 ± 4.5	777 ± 102	92 ± 4.5	8.3 ± 1.4	8.6 ± 1.4	4.4 ± 0.5	91.4 ± 0.9	59.8 ± 2.6
2a	8	60.8 ± 4	4/4	2/2/3/1	51.9 ± 4.9	849 ± 152	95.9 ± 4.8	7.6 ± 1.4	11.1 ± 1.7	4.4 ± 0.6	89.6 ± 2.8	60.1 ± 2.8
2b	8	52.8 ± 6.6	6/2	1/3/3/1	49 ± 4	902 ± 189	92.4 ± 2.4	4.8 ± 1.1	7.2 ± 1.3	4.0 ± 0.4	92.4 ± 2.4	62.5 ± 1.7
2c	6	56.8 ± 5.9	4/2	0/2/2/2	44.2 ± 3.5	856 ± 123	96.3 ± 3.9	5 ± 1.1	6 ± 1	3.8 ± 0.3	92.8 ± 1.5	63.6 ± 1.8
2d	6	51.2 ± 3.8	4/2	2/2/2/0	55.5 ± 4.9	940 ± 110	91.2 ± 8.1	11.2 ± 1.2	10 ± 0.7	3.9 ± 0.4	92 ± 1.9	62 ± 5.8
2e	3	57.3 ± 9.1	1/2	0/1/0/2	45.3 ± 5.2	769 ± 267	99 ± 3.2	5 ± 2.1	9 ± 0.6	4.5 ± 0.6	94.2 ± 1.3	66.3 ± 1.5
3a	6	52.7 ± 6.6	4/2	2/4/0/0	53.8 ± 6.7	928 ± 145	92.7 ± 7.9	8.7 ± 2.7	8.8 ± 1.3	4.2 ± 0.6	90.4 ± 2.8	64.8 ± 4.3
3b	6	58.3 ± 3.5	4/2	3/1/1/1	54.2 ± 6.1	808 ± 156	94.3 ± 2.8	7 ± 1.4	10 ± 1.3	5 ± 0.7	91.9 ± 0.7	63.5 ± 2.9
3c	21	57.4 ± 5.6	8/3	7/7/6/1	46.1 ± 2.5	900 ± 99	88 ± 2.8	9 ± 1.4	9.2 ± 0.5	3.7 ± 0.3	91.7 ± 0.5	59.7 ± 2
3d	7	55.6 ± 5.8	3/4	0/4/3/0	53.1 ± 7.1	732 ± 123	91.4 ± 5.6	7.9 ± 3.1	8.6 ± 1.3	5 ± 0.4	90.7 ± 1.4	61.3 ± 3.7
3e	8	59 ± 5.2	7/1	0/4/4/0	45.1 ± 3.9	733 ± 114	92.8 ± 6.8	4.6 ± 0.8	8.1 ± 1.1	4.3 ± 0.2	90.7 ± 0.8	66.3 ± 2.8

Group 1 corresponds to study i); randomized crossover study comparing inhaled iloprost (ILO) and inhaled treprostinil (TRE).

a = 7.5 g ILO vs. 7.5 µg TRE,

b = 7.5 g ILO vs. 15 µg TRE (6 min inhalation time),

c = 7.5 g ILO vs. 15 µg TRE (3 min inhalation time).

Group 2 corresponds to study ii); evaluation of maximal tolerated dose of TRE.

a = placebo inhalation,

b = 30 µg TRE,

c = 60 µg TRE,

d = 90 µg TRE,

e = 120 µg TRE.

Group 3 corresponds to study iii); reduction of inhalation time by increase of TRE concentration, aiming at a total inhaled dose of 15 µg.

a = 18 pulses of 100 µg/ml TRE,

b = 9 pulses of 200 µg/ml TRE,

c = 3 pulses of 600 µg/ml TRE,

d = 2 pulses of 1000 µg/ml TRE,

e = 1 pulse 2000 µg/ml TRE.

Etiology of pulmonary hypertension was classified as idiopathic PAH (i), PAH of other causes (o), chronic thromboembolic PH (t), and pulmonary fibrosis (f).

Each patient inhaled both iloprost and treprostinil on the same day during right heart catheter investigation; the drugs were administered consecutively with a one hour interval between the drug applications. One half of the study patients initially inhaled treprostinil and then inhaled iloprost (n=22), while the other half initially inhaled iloprost and then inhaled treprostinil (n=22). Patients were randomized to one of the two groups and blinded as to the study drugs. Drug effects were monitored for 60 minutes after each inhalation. Iloprost was inhaled at 4 µg/ml (6 min inhalation time; n=44) and treprostinil was inhaled at a concentration of 4 µg/ml (6 min inhalation; n=14), 8 µg/ml (6 min inhalation; n=14) or 16 µg/ml (3 min inhalation; n=16). Based on previous biophysical characterization of the ultrasonic device with iloprost- and treprostinil-solution, this corresponds to a total inhaled dose of 7.5 µg iloprost and treprostinil (4 µg/ml) and 15 µg treprostinil (8 µg/ml and 16 µg/ml), respectively.

Study ii) was a randomized, open-label, single blind, placebo controlled study. The primary objectives were to describe the pharmacodynamic and pharmacokinetic effects of inhaled treprostinil at a well tolerated dose (30 µg) and to explore the highest tolerated single dose. A total number of 31 patients inhaled either placebo or treprostinil; each patient received one inhalation. The first 16 patients were randomized to 30 µg TRE (16 µg/ml, n=8) or placebo (stock solution in a concentration corresponding to TRE 16 µg/ml). Subsequent patients received 60 µg TRE (32 µg/ml; n=6), 90 µg TRE (48 µg/ml; n=6) and 120 µg TRE (64 µg/ml; n=3). Inhalation time was 6 minutes in all groups. Hemodynamics and gas-exchange as well as arterial treprostinil concentrations were recorded for 180 minutes.

Study iii) was a randomized, open-label, single blind study. The primary objective was to explore the shortest possible inhalation time for a 15 µg dose of inhaled treprostinil. A total

of 48 patients inhaled one dose of TRE during right heart catheter investigation. The drug was applied in 18, 9, 3, 2 or 1 breaths. The aerosol was generated by a pulsed ultrasonic nebulizer (OPTINEB® NebuteC, Elsenfeld, Germany) in cycles consisting of 2 seconds aerosol production (pulse) and 4 seconds pause. The device included an opto-acoustical trigger for the patient to synchronize the inspiration to the end of the aerosol pulse, thereby providing exact dosage. The TRE dose of 15 µg was either generated during 18 cycles (OPTINEB® filled with 100 µg/ml TRE, n=6), 9 cycles (200 µg/ml TRE, n=6), 3 cycles (600 µg/ml TRE, n=21), 2 cycles (1000 µg/ml TRE, n=7) or 1 cycle (2000 µg/ml TRE, n=8). Hemodynamics and gas exchange were recorded for 120-180 minutes.

Treprostinil plasma concentrations were assessed in study ii) at 10, 15, 30, 60 and 120 minutes after inhalation. Treprostinil quantification was done by Alta Analytical Laboratory (El Dorado Hills, Calif., USA) with a validated liquid chromatography atmospheric-pressure ionization tandem mass spectrometry as previously described Wade M., et al. J. Clin. Pharmacol. 2004; 44:503-9. Mixed venous blood was drawn at the depicted time points (FIG. 11) after inhalation, centrifuged and the plasma frozen at -80° C. until temperature controlled shipping on dry ice.

Statistics:

For statistical analysis of study i) the repeated PVR measurements after inhaled iloprost and treprostinil were subjected to a three-factorial analysis of variance (ANOVA; factors: time (A), drug (B), treprostinil concentration (C)) to avoid multiple testing. The time to maximum PVR decrease after inhalation of iloprost versus treprostinil was compared by paired t-test. Area under the curve (AUC) was calculated from start of inhalation until 60 min after inhalation. Means, standard error of the mean (SEM) and 95% confidence inter-

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vals were calculated. For study ii) and iii) areas between curves (ABC) were calculated between placebo inhalation (study ii) and the respective treprostinil inhalation until 180 min (study ii)) and 120 min (study iii)) after end of inhalation. Results:

The inhalation of iloprost as well as treprostinil in study i) resulted in a rapid decrease in PVR and PAP (FIG. 5-7). No significant differences were observed for the areas under the curve (AUC) of PVR decrease after inhalation of 7.5 µg TRE in 6 minutes (AUC $-12.6 \pm 7.0\%$), 15 µg TRE in 6 minutes (AUC $-13.3 \pm 3.2\%$) and 15 µg TRE in 3 minutes (AUC $-13.6 \pm 4.3\%$). The AUC for PVR after the inhalation of 7.5 µg iloprost in 6 minutes was $-7.7 \pm 3.7\%$ (mean \pm 95% confidence interval). An overview of the pooled data of treprostinil inhalation as compared to iloprost inhalation is given in FIG. 7. The maximum effect of iloprost and treprostinil on PVR was comparable but this effect was reached significantly later after treprostinil inhalation (18 ± 2 min) compared to iloprost (8 ± 1 min; mean \pm SEM, $p < 0.0001$) and lasted considerably longer (after 60 min, PVR values in the treprostinil group had not yet returned to baseline). The increase in cardiac output was less acute but prolonged after treprostinil inhalation. Systemic arterial pressure (SAP) was unaffected by treprostinil inhalation, whereas a transient decrease was observed after iloprost inhalation. Iloprost and treprostinil did not affect gas exchange. Three-factorial ANOVA for PVR demonstrated a significant difference between repeated measurements after inhalation ($p_{(A)} < 0.0001$), no significant difference between drugs ($p_B = 0.1$), no difference between treprostinil concentrations ($p_{(C)} = 0.74$) and a significant drug \times time interaction ($p_{(A \times B)} < 0.0001$). This translates into a significant effect of both drugs on PVR with comparable drug potency but a prolonged drug effect of treprostinil compared to iloprost.

In this study the occasionally observed mild side effects of iloprost inhalation at the given dose (transient flush, headache) were not observed with inhaled treprostinil. Bad taste was reported by most of the patients after inhalation of TRE. This was later found to be attributable to the metacresol preservative contained in the treprostinil solution.

In study ii) pharmacodynamics of inhaled placebo or treprostinil were observed for 180 minutes. Placebo inhalation was followed by a gradual increase in PVR over the entire observation time. Due to reduced patient numbers in the 120 µg TRE group (because of side effects, see below), the hemodynamic values for this group were not included in the graphs of this study (FIG. 8-9). All TRE doses lead to comparable maximal decreases of PVR to $76.5 \pm 4.7\%$ (30 µg), $73.7 \pm 5.8\%$ (60 µg), $73.3 \pm 4.3\%$ (90 µg) and $65.4 \pm 4.1\%$ (120 µg) of baseline values. An extended duration of pulmonary vasodilation was noted, surpassing the 3 hour observation period for the 60 µg and 90 µg (and 120 µg) TRE doses, whereas in the 30 µg dose group the hemodynamic changes had just returned to baseline within this period. Even at the highest doses, TRE had only minor effects on systemic arterial pressure (FIG. 8). Cardiac output was increased to a maximum of $106.8 \pm 3.2\%$ (30 µg), $122.9 \pm 4.3\%$ (60 µg), $114.3 \pm 4.8\%$ (90 µg) and $111.3 \pm 3.9\%$ (120 µg TRE). The areas between the response curves after placebo versus TRE inhalation were calculated for PVR, PAP, SVR and SAP (FIG. 9). Areas between the curves for PVR were not significantly different for 30 µg, 60 µg and 90 µg TRE, a nearly maximal effect on PVR was already observed with 30 µg TRE. Effects on PAP and SAP were small and did not show a dose-response relationship. Gas exchange was not affected at doses up to 90 µg TRE, but arterial oxygen saturation was significantly decreased at a

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dose of 120 µg TRE in all 3 patients. Further dose increments were omitted due to this side effect and severe headache in one patient.

Again, bad taste of the TRE aerosol was reported by most patients. Other side effects were flushing ($n=1$; 30 µg TRE), mild transient cough ($n=3$; 60 µg TRE), mild transient bronchoconstriction that resolved after one inhalation of fenoterol ($n=1$; 30 µg TRE), moderate bronchoconstriction that resolved after one inhalation of fenoterol ($n=1$; 120 µg TRE), and severe headache ($n=1$; 120 µg TRE). The bad taste, the bronchoconstriction and the drop in SaO₂ was attributed to metacresol in the original TRE solution. With the use of a metacresol-free solution of TRE (University Hospital Gießen, Germany; produced according to the manufacturer's protocol) in the following study, these side effects did no longer occur.

Study iii) was performed with metacresol-free TRE solution, having no specific taste and smell. A total of 48 patients were enrolled. This study aimed at the reduction of inhalation time and aerosol volume needed for pulmonary drug delivery. A modified OPTINEB® inhalation device was programmed to produce a constant amount of aerosol during repeatable pulses of aerosol generation. With this device, treprostinil could be safely utilized up to a concentration of 2000 µg/ml without considerable side effects. No relationship of number or type of side effects to TRE concentration was observed. Reported side effects were mild transient cough ($n=6$), mild headache ($n=2$) and mild jaw pain ($n=1$).

The reduction of PVR and PAP was comparable between all groups (FIG. 10). TRE inhalation reduced PVR to $76.3 \pm 5.6\%$ (18 pulses, 100 µg/ml), $72.9 \pm 4.9\%$ (9 pulses, 200 µg/ml), $71.2 \pm 6.0\%$ (3 pulses, 600 µg/ml), $77.4 \pm 4.5\%$ (2 pulses, 1000 µg/ml) and $80.3 \pm 5.2\%$ (1 pulse, 2000 µg/ml). PAP was reduced to $84.2 \pm 4.5\%$ (18 pulses, 100 µg/ml), $84.2 \pm 4.1\%$ (9 pulses, 200 µg/ml), $81.1 \pm 4.1\%$ (3 pulses, 600 µg/ml), $86 \pm 4\%$ (2 pulses, 1000 µg/ml) and $88 \pm 5.4\%$ (1 pulse, 2000 µg/ml). Cardiac output was moderately increased in all groups, whereas systemic arterial pressure was not significantly affected.

The areas between the curves (ABC) for changes in hemodynamic and gas-exchange parameters after inhalation of 15 µg TRE versus placebo were calculated for an observation time of 120 minutes (FIG. 11). The ABC for both PVR and PAP was comparable between all groups.

Pharmacokinetic results from study ii): Peak plasma concentrations of treprostinil were found 10-15 minutes after inhalation. Maximal treprostinil plasma concentrations (C_{max}) for the 30 µg, 60 µg, 90 µg and 120 µg doses were 0.65 ± 0.28 ng/ml ($n=4$), 1.59 ± 0.17 ng/ml ($n=4$), 1.74 ng/ml ($n=1$) and 3.51 ± 1.04 ng/ml ($n=2$), respectively (mean \pm SEM; FIG. 12).

Discussion:

These studies investigated whether i) the acute effects of inhaled treprostinil would be comparable to or possibly advantageous over inhaled iloprost in pulmonary hypertensive patients, ii) the inhaled prostanoid dose might be increased without substantial local or systemic side effects, and iii) if the time of inhalation, which is 6-12 minutes for iloprost, could be reduced significantly by increasing the concentration of treprostinil aerosol.

The patient population in these studies included different forms of precapillary pulmonary hypertension. All these patients had a need for therapy of pulmonary hypertension and reflected the typical population of a pulmonary hypertension center. No major differences in patient characteristics or hemodynamic baseline values existed between the different groups (table 3).

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In study i) it was shown that the inhalation of treprostinil and iloprost in similar doses resulted in a comparable maximum pulmonary vasodilatory effect. However, marked differences in the response profile were noted. The onset of the pulmonary vasodilatory effect of inhaled treprostinil was delayed compared to iloprost, but lasted considerably longer, with the PVR decrease continuing beyond the one-hour observation period. Although the average dose of treprostinil was higher than the iloprost dose, no systemic effects were noted after treprostinil inhalation, whereas flush and transient SAP decrease, accompanied by more prominent cardiac output increase, occurred after iloprost inhalation. Such side effects were more prominent than in previous studies with inhaled iloprost. This may have been caused by the fact that the iloprost dose used in this study was 50% higher than the recommended single inhalation dose (5 µg) and that the preceding treprostinil inhalation may have added to the systemic side effects caused by the iloprost inhalation. Surprisingly, with TRE there was no such systemic side effect, although the average effect on PVR was as potent as with iloprost.

This study used a cross-over design in order to minimize the effects of inter-individual differences in response to prostanooids. The short observation period of 1 hour was used to avoid an uncomfortably long catheter investigation. As a study limitation, the short observation interval may have caused carryover effects of the first to the second period as suggested by FIG. 5. However, this still allowed for the interpretation of the study, that both drugs are potent pulmonary vasodilators and that treprostinil effects are significantly sustained compared to the iloprost effects.

The longer duration of action and the virtual absence of side effects (except the bitter taste of treprostinil aerosol, later attributed to metacresol) encouraged increasing the applied treprostinil dose in study ii). Observation time was extended to 3 hours to obtain precise pharmacodynamic data. Inhaled treprostinil resulted in a strong pulmonary vasodilation that outlasted the observation time of 3 hours when compared to placebo inhalation. Surprisingly, inhaled treprostinil was tolerated in doses up to 90 µg.

Study iii) successfully demonstrated that the inhalation time could be reduced to literally one single breath of 2000 µg/ml treprostinil solution, thereby applying a dose of 15 µg. This drug administration with a single breath induced pulmonary vasodilation for longer than 3 hours compared to placebo inhalation. Side effects were minor, of low frequency and not related to drug concentration. It was a surprising finding that such high concentrations of treprostinil were so well tolerated.

CONCLUSION

Inhaled treprostinil can be applied in high doses (up to 90 µg) with a minimal inhalation time. Inhaled treprostinil exerts high pulmonary selectivity and leads to a long-lasting pulmonary vasodilation.

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Although the foregoing refers to particular preferred embodiments, it will be understood that the present invention is not so limited. It will occur to those of ordinary skill in the art that various modifications may be made to the disclosed embodiments and that such modifications are intended to be within the scope of the present invention.

All of the publications, patent applications and patents cited in this specification are incorporated herein by reference in their entirety.

What is claimed is:

1. A kit for treating pulmonary hypertension comprising:
 - (i) a formulation comprising 200 to 1000 µg/ml treprostinil or a pharmaceutically acceptable salt thereof;
 - (ii) a pulsed ultrasonic nebulizer comprising an opto-acoustical trigger, configured to
 - (a) aerosolize a fixed amount of treprostinil per pulse, and
 - (b) deliver by inhalation a therapeutically effective single event dose of said formulation, said single event dose comprising 15 µg to 90 µg treprostinil or a pharmaceutically acceptable salt thereof delivered in 1 to 18 breaths; and
 - (iii) instructions for using the pulsed ultrasonic nebulizer with the formulation to treat a patient with pulmonary hypertension by delivering 15 µg to 90 µg treprostinil or a pharmaceutically acceptable salt thereof in 1 to 18 breaths to the patient in the single event dose.
2. The kit of claim 1, wherein the formulation comprises 600 µg/ml of the treprostinil or its pharmaceutically acceptable salt thereof.
3. The kit of claim 1, further comprising instructions for the human not to repeat the single event dose for a period of at least 3 hours.
4. The kit of claim 1, wherein the single event dose produces a peak plasma concentration of treprostinil about 10-15 minutes after the single event dose.
5. The kit of claim 1, wherein the fixed amount of treprostinil or its pharmaceutically salt for each breath inhaled by the human comprises at least 5 ng of treprostinil or its pharmaceutically acceptable salt.
6. The kit of claim 2, wherein the fixed amount of treprostinil or its pharmaceutically salt for each breath inhaled by the human comprises at least 5 ng of treprostinil or its pharmaceutically acceptable salt.
7. The kit of claim 1, wherein the single event dose is inhaled in 3 to 18 breaths by the human.
8. The kit of claim 6, wherein the single event dose is inhaled in 3 to 18 breaths by the human.
9. The kit of claim 6, further comprising instructions for the human not to repeat the single event dose for a period of at least 3 hours.

* * * * *

EXHIBIT 15

(12) **United States Patent**
Olschewski et al.(10) **Patent No.: US 10,376,525 B2**(45) **Date of Patent: *Aug. 13, 2019**(54) **TREPROSTINIL ADMINISTRATION BY
INHALATION**(71) Applicant: **United Therapeutics Corporation,**
Silver Spring, MD (US)(72) Inventors: **Horst Olschewski**, Graz (AT); **Robert
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Giessen (DE)(73) Assignee: **United Therapeutics Corporation,**
Silver Spring, MD (US)(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.This patent is subject to a terminal dis-
claimer.(21) Appl. No.: **15/011,999**(22) Filed: **Feb. 1, 2016**(65) **Prior Publication Data**

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Related U.S. Application Data(60) Division of application No. 13/469,854, filed on May
11, 2012, now Pat. No. 9,339,507, which is a division
of application No. 12/591,200, filed on Nov. 12, 2009,
now Pat. No. 9,358,240, which is a continuation of
application No. 11/748,205, filed on May 14, 2007,
now abandoned.(60) Provisional application No. 60/800,016, filed on May
15, 2006.(51) **Int. Cl.****A61K 31/192** (2006.01)**A61P 9/12** (2006.01)**A61M 11/00** (2006.01)**A61K 31/557** (2006.01)**A61K 9/00** (2006.01)(52) **U.S. Cl.**CPC **A61K 31/557** (2013.01); **A61K 9/008**
(2013.01); **A61K 9/0078** (2013.01); **A61K**
31/192 (2013.01)(58) **Field of Classification Search**USPC 514/573, 569
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U.S. Pat. No. 9,339,507, with all Exhibits on exhibit list.*Watson Laboratories, Inc.* (Petitioner) v. *United Therapeutics, Inc.*
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Primary Examiner — Jeffrey S Lundgren*Assistant Examiner* — Michael J Schmitt(74) *Attorney, Agent, or Firm* — Foley & Lardner LLP(57) **ABSTRACT**Treprostinil can be administered using a metered dose
inhaler. Such administration provides a greater degree of
autonomy to patients. Also disclosed are kits that include a
metered dose inhaler containing a pharmaceutical formula-
tion containing treprostinil.**4 Claims, 12 Drawing Sheets**

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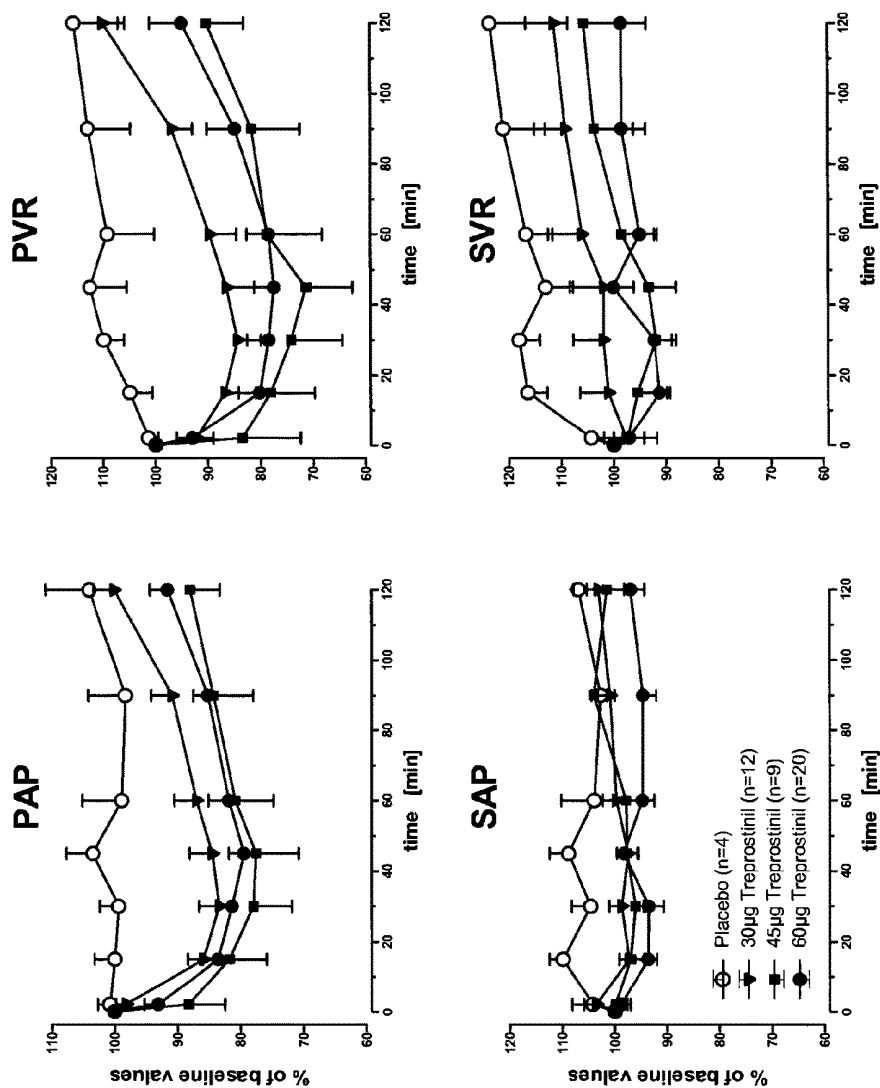
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FIGURE 1



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FIGURE 2

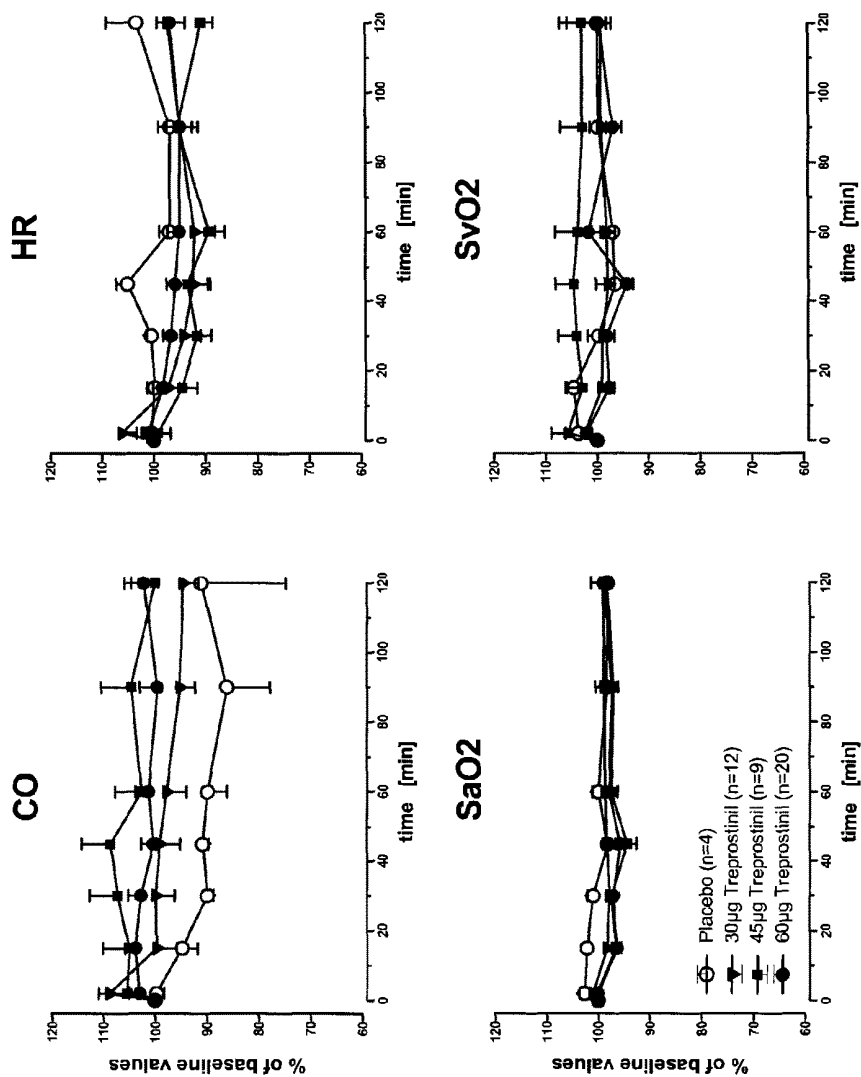


FIGURE 3

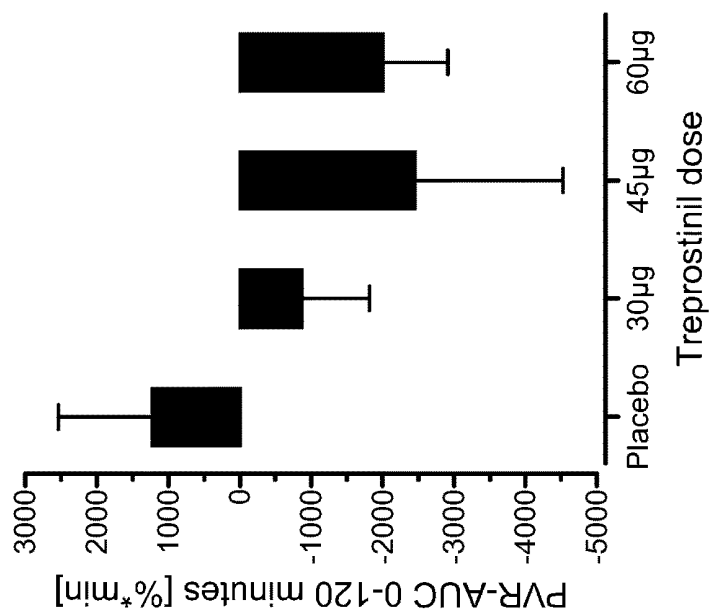
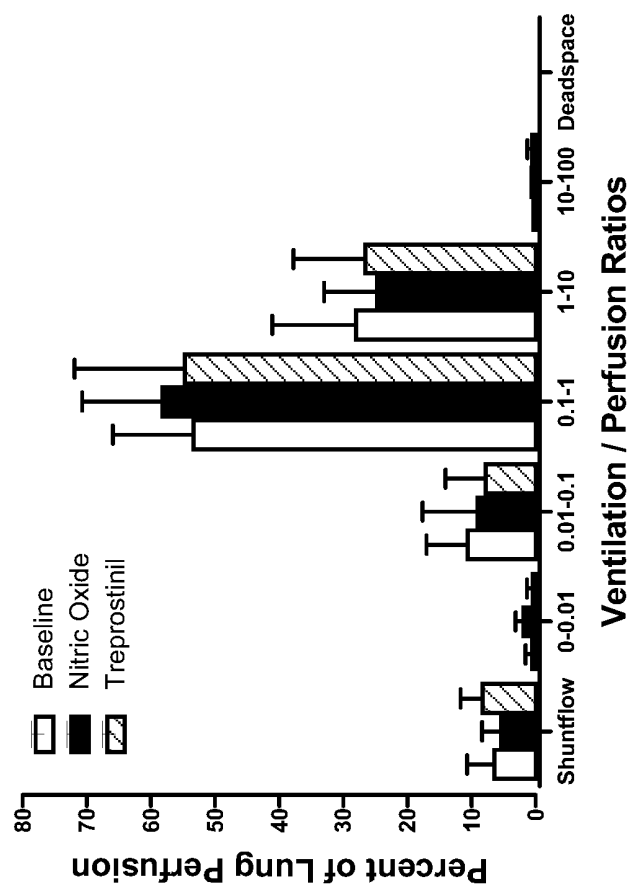


FIGURE 4



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FIGURE 5

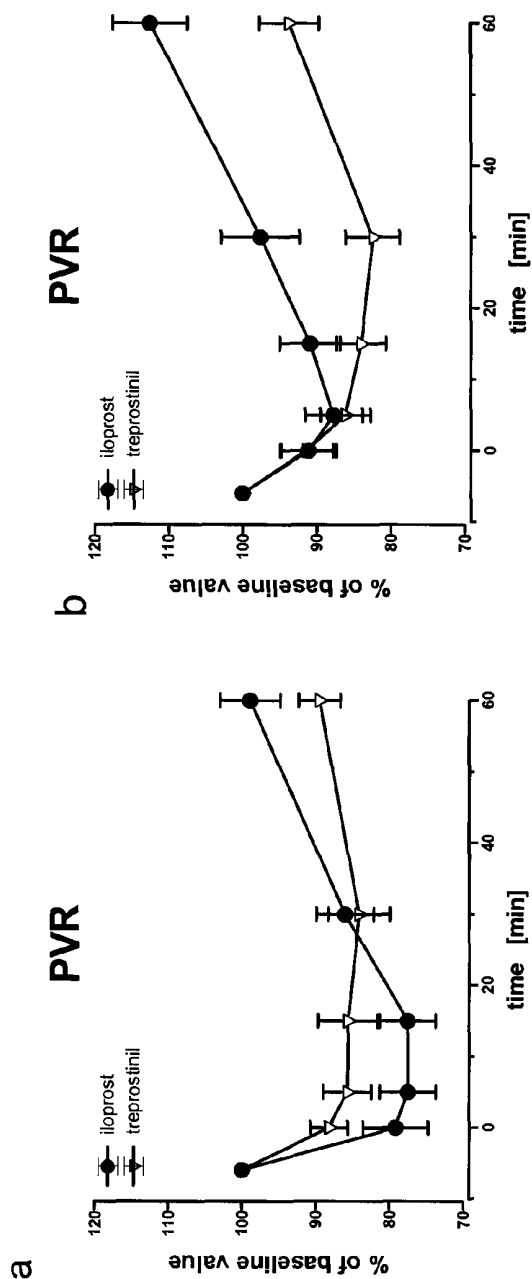
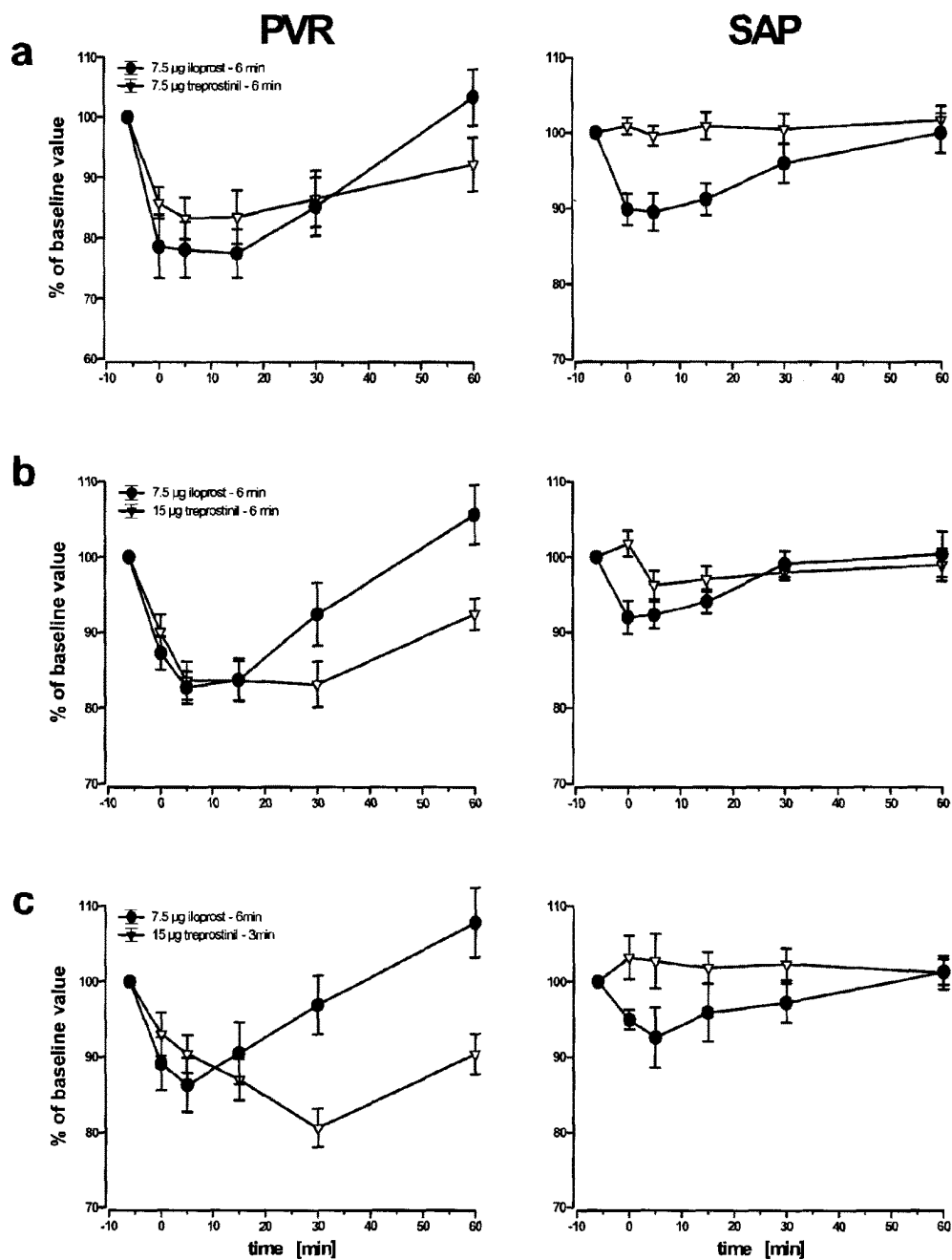


FIGURE 6



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FIGURE 7

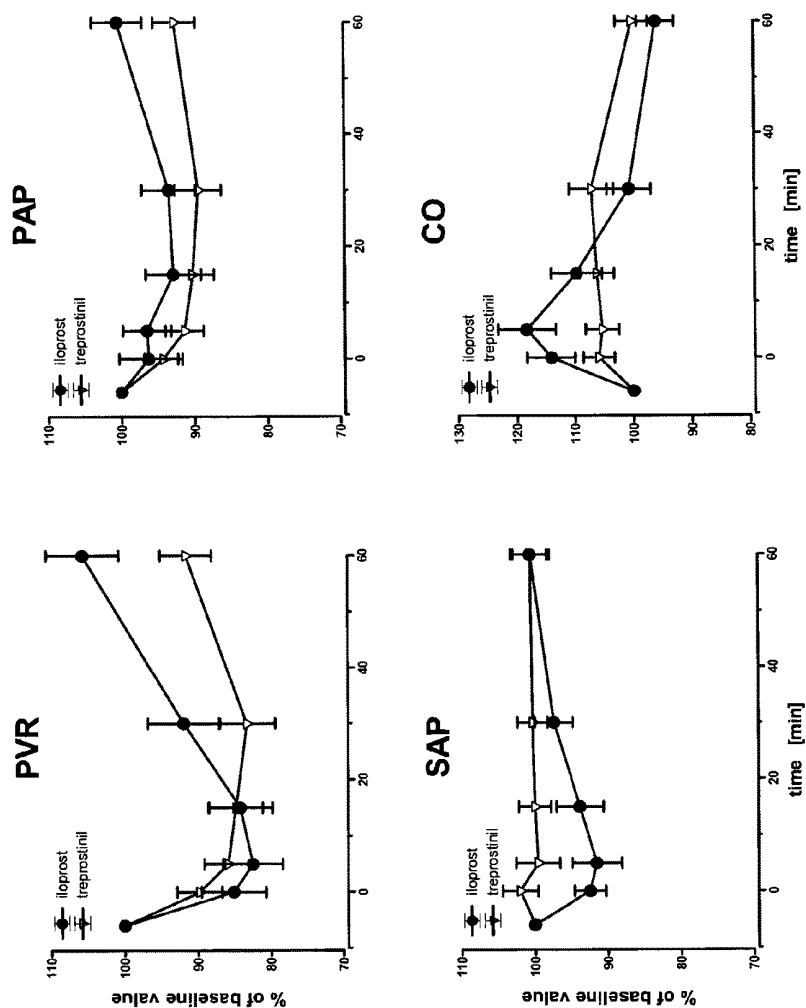


FIGURE 8

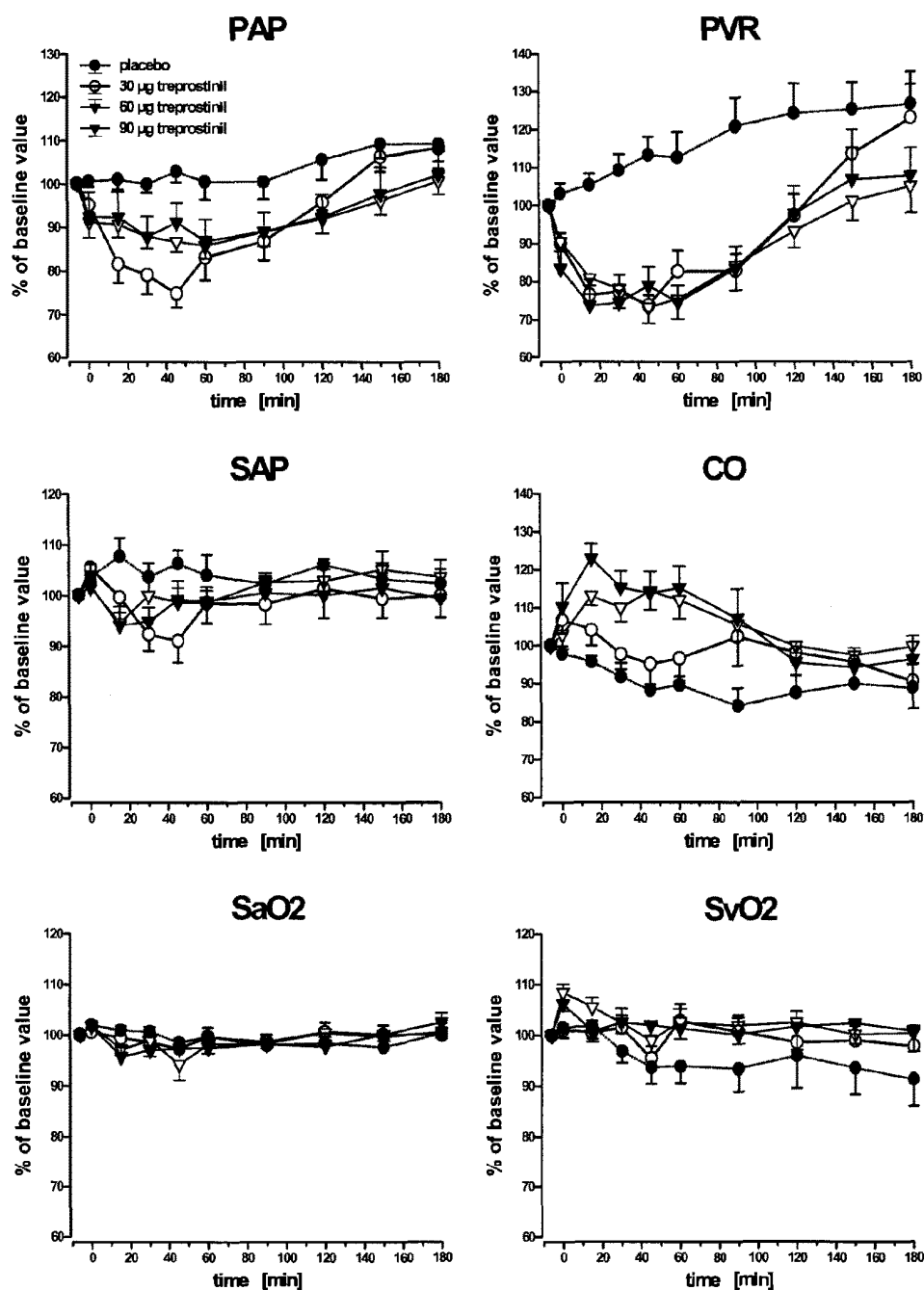
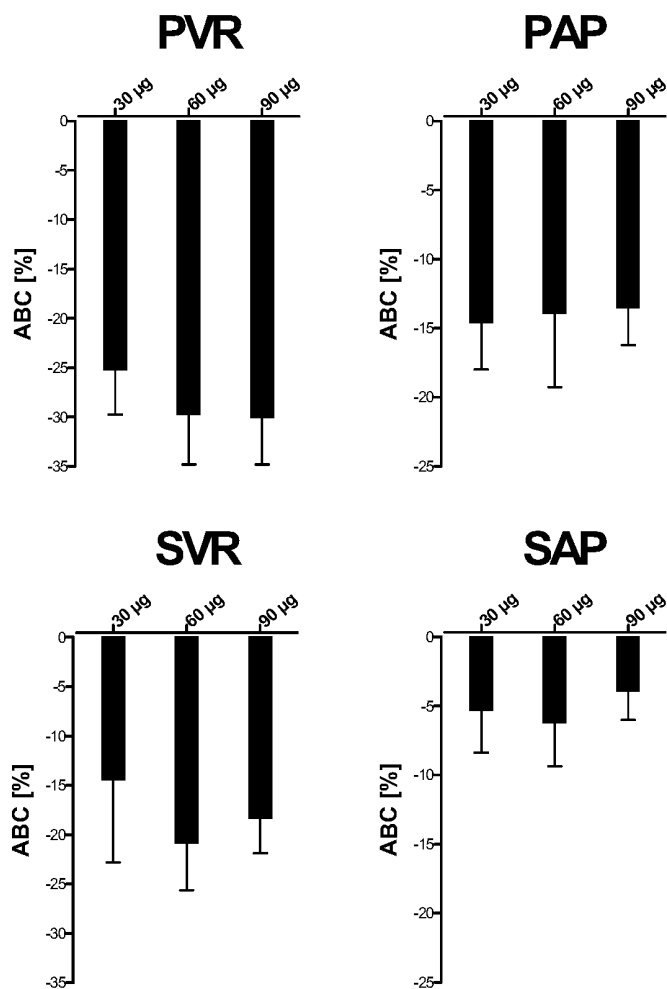


FIGURE 9



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FIGURE 10

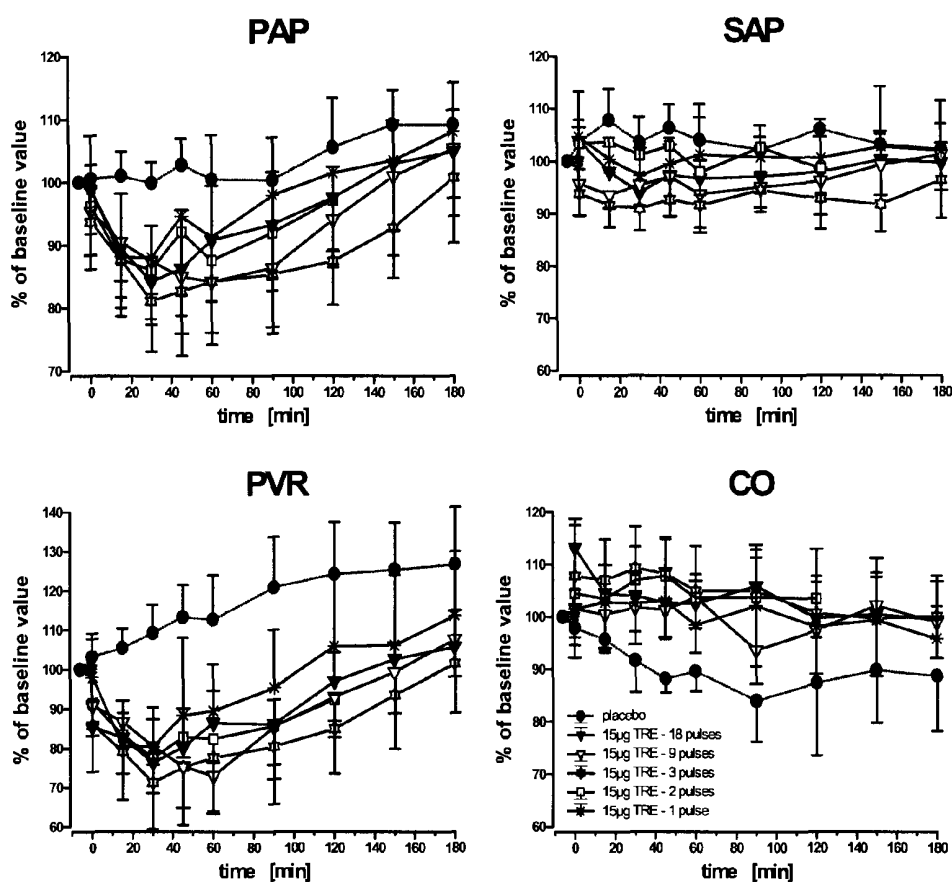


FIGURE 11

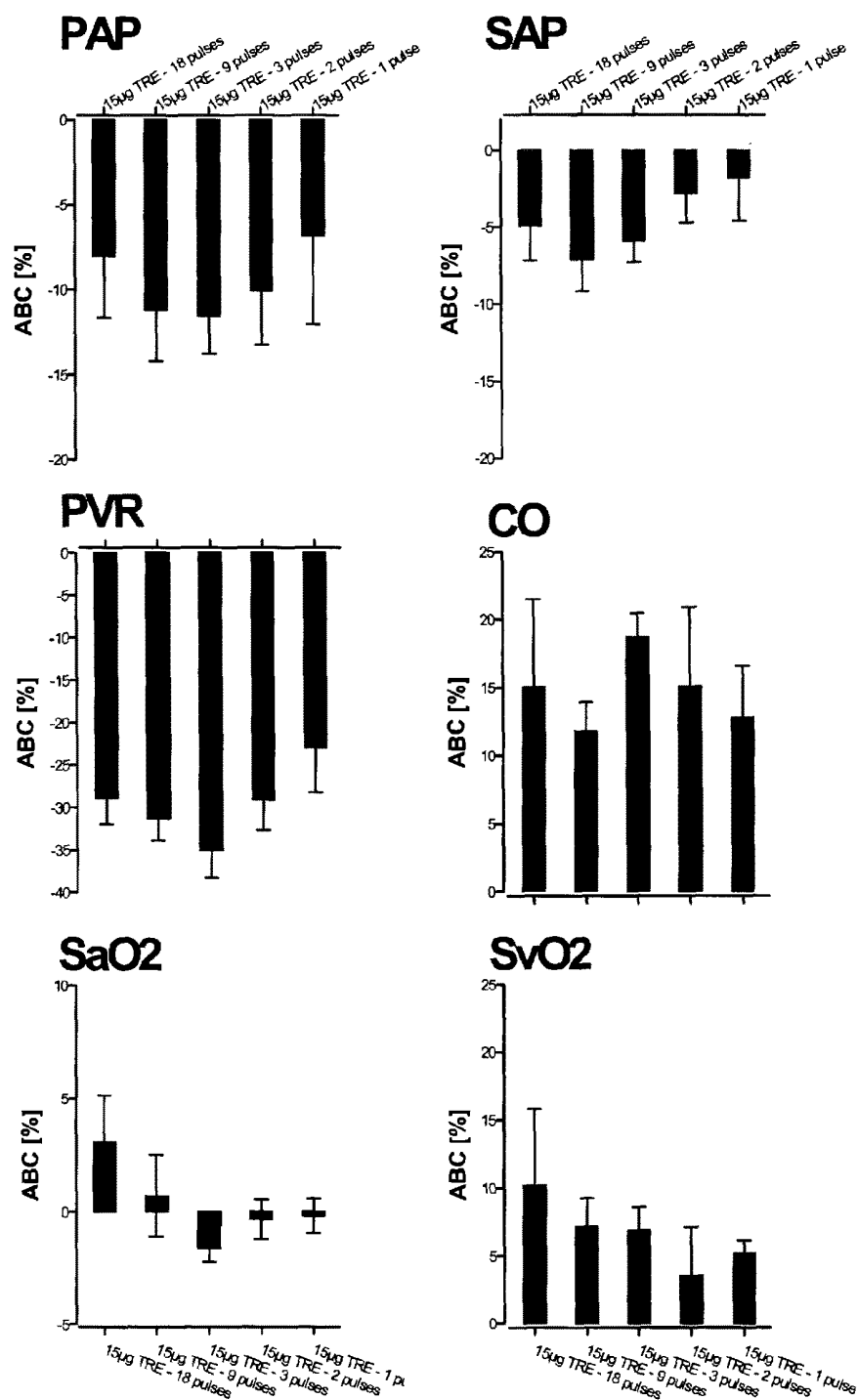
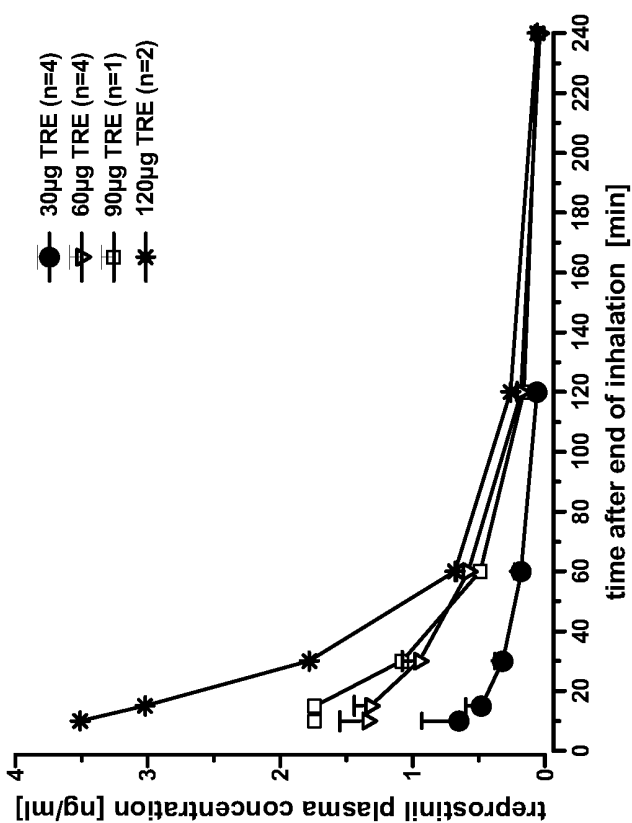


FIGURE 12



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TREPROSTINIL ADMINISTRATION BY INHALATION

CROSS REFERENCE TO RELATED APPLICATIONS

The present application is a Divisional of U.S. application Ser. No. 13/469,854, filed May 11, 2012, Divisional of U.S. application Ser. No. 12/591,200, filed Nov. 12, 2009, which is a Continuation of U.S. application Ser. No. 11/748,205, filed May 14, 2007, which claims priority to U.S. provisional application No. 60/800,016 filed May 15, 2006, which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

The present application relates to methods and kits for therapeutic treatment and, more particularly, to therapeutic methods involving administering treprostinil using a metered dose inhaler and related kits.

BACKGROUND OF THE INVENTION

All blood is driven through the lungs via the pulmonary circulation in order, among other things, to replenish the oxygen which it dispenses in its passage around the rest of the body via the systemic circulation. The flow through both circulations is in normal circumstances equal, but the resistance offered to it in the pulmonary circulation is generally much less than that of the systemic circulation. When the resistance to pulmonary blood flow increases, the pressure in the circulation is greater for any particular flow. The above described condition is referred to as pulmonary hypertension (PH). Generally, pulmonary hypertension is defined through observations of pressures above the normal range pertaining in the majority of people residing at the same altitude and engaged in similar activities.

Pulmonary hypertension may occur due to various reasons and the different entities of pulmonary hypertension were classified based on clinical and pathological grounds in 5 categories according to the latest WHO convention, see e.g. Simonneau G., et al. J. Am. Coll. Cardiol. 2004; 43(12 Suppl S):S5-S12S. Pulmonary hypertension can be a manifestation of an obvious or explicable increase in resistance, such as obstruction to blood flow by pulmonary emboli, malfunction of the heart's valves or muscle in handling blood after its passage through the lungs, diminution in pulmonary vessel caliber as a reflex response to alveolar hypoxia due to lung diseases or high altitude, or a mismatch of vascular capacity and essential blood flow, such as shunting of blood in congenital abnormalities or surgical removal of lung tissue. In addition, certain infectious diseases, such as HIV and liver diseases with portal hypertension may cause pulmonary hypertension. Autoimmune disorders, such as collagen vascular diseases, also often lead to pulmonary vascular narrowing and contribute to a significant number of pulmonary hypertension patients. The cases of pulmonary hypertension remain where the cause of the increased resistance is as yet inexplicable are defined as idiopathic (primary) pulmonary hypertension (iPAH) and are diagnosed by and after exclusion of the causes of secondary pulmonary hypertension and are in the majority of cases related to a genetic mutation in the bone morphogenetic protein receptor-2 gene. The cases of idiopathic pulmonary arterial hypertension tend to comprise a recognizable entity of about 40% of patients cared for in large specialized pulmonary hypertension centers. Approximately

65% of the most commonly afflicted are female and young adults, though it has occurred in children and patients over 50. Life expectancy from the time of diagnosis is short without specific treatment, about 3 to 5 years, though occasional reports of spontaneous remission and longer survival are to be expected given the nature of the diagnostic process. Generally, however, disease progress is inexorable via syncope and right heart failure and death is quite often sudden.

Pulmonary hypertension refers to a condition associated with an elevation of pulmonary arterial pressure (PAP) over normal levels. In humans, a typical mean PAP is approximately 12-15 mm Hg. Pulmonary hypertension, on the other hand, can be defined as mean PAP above 25 mmHg, assessed by right heart catheter measurement. Pulmonary arterial pressure may reach systemic pressure levels or even exceed these in severe forms of pulmonary hypertension. When the PAP markedly increases due to pulmonary venous congestion, i.e. in left heart failure or valve dysfunction, plasma can escape from the capillaries into the lung interstitium and alveoli. Fluid buildup in the lung (pulmonary edema) can result, with an associated decrease in lung function that can in some cases be fatal. Pulmonary edema, however, is not a feature of even severe pulmonary hypertension due to pulmonary vascular changes in all other entities of this disease.

Pulmonary hypertension may either be acute or chronic. Acute pulmonary hypertension is often a potentially reversible phenomenon generally attributable to constriction of the smooth muscle of the pulmonary blood vessels, which may be triggered by such conditions as hypoxia (as in high-altitude sickness), acidosis, inflammation, or pulmonary embolism. Chronic pulmonary hypertension is characterized by major structural changes in the pulmonary vasculature, which result in a decreased cross-sectional area of the pulmonary blood vessels. This may be caused by, for example, chronic hypoxia, thromboembolism, collagen vascular diseases, pulmonary hypercirculation due to left-to-right shunt, HIV infection, portal hypertension or a combination of genetic mutation and unknown causes as in idiopathic pulmonary arterial hypertension.

Pulmonary hypertension has been implicated in several life-threatening clinical conditions, such as adult respiratory distress syndrome ("ARDS") and persistent pulmonary hypertension of the newborn ("PPHN"). Zapol et al., Acute Respiratory Failure, p. 241-273, Marcel Dekker, New York (1985); Peckham, J. Ped. 93:1005 (1978). PPHN, a disorder that primarily affects full-term infants, is characterized by elevated pulmonary vascular resistance, pulmonary arterial hypertension, and right-to-left shunting of blood through the patent ductus arteriosus and foramen ovale of the newborn's heart. Mortality rates range from 12-50%. Fox, Pediatrics 59:205 (1977); Dworetz, Pediatrics 84:1 (1989). Pulmonary hypertension may also ultimately result in a potentially fatal heart condition known as "cor pulmonale," or pulmonary heart disease. Fishman, "Pulmonary Diseases and Disorders" 2nd Ed., McGraw-Hill, New York (1988).

Currently, there is no treatment for pulmonary hypertension that can be administered using a compact inhalation device, such as a metered dose inhaler.

SUMMARY OF THE INVENTION

One embodiment is a method of delivering to a subject in need thereof a therapeutically effective amount of treprostinil, or treprostinil derivative or a pharmaceutically acceptable salt thereof comprising administering to the subject a

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therapeutically effective amount of the treprostinil or treprostinil derivative or a pharmaceutically acceptable salt thereof using a metered dose inhaler.

Another embodiment is a method for treating pulmonary hypertension comprising administering to a subject in need thereof treprostinil or its derivative, or a pharmaceutically acceptable salt thereof using a metered dose inhaler.

Yet another embodiment is a kit comprising a metered dose inhaler containing a pharmaceutical formulation comprising treprostinil or treprostinil derivative, or a pharmaceutically acceptable salt thereof.

And yet another embodiment is a kit for treating pulmonary hypertension in a subject, comprising (i) an effective amount of treprostinil or its derivative, or a pharmaceutically acceptable salt thereof; (ii) a metered dose inhaler; (iii) instructions for use in treating pulmonary hypertension.

Administration of treprostinil using a metered dose inhaler can provide patients, such as pulmonary hypertension patients, with a high degree of autonomy.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 pulmonary and systemic changes in hemodynamics following the inhalation of placebo (open circles), 30 µg treprostinil (triangles), 45 µg treprostinil (squares) or 60 µg TREprostinil (black circles) applied by a Metered Dose Inhaler (MDI-TRE). A single short inhalation of treprostinil induced sustained reduction of PAP and PVR that outlasted the observation period of 120 minutes at doses of 45 and 60 µg MDI-TRE. Systemic arterial pressure and resistance were not significantly affected. PAP=mean pulmonary artery pressure; PVR=pulmonary vascular resistance; SAP=mean systemic arterial pressure; SVR=systemic vascular resistance. Data are given as mean value±standard error of the mean (SEM).

FIG. 2 presents hemodynamic changes induced by the inhalation of placebo (open circles), 30 µg treprostinil (triangles), 45 µg treprostinil (squares) or 60 µg treprostinil (black circles) applied by a metered dose inhaler. Treprostinil induced sustained elevation of cardiac output. Heart rate was rather unchanged as a sign for low spillover of MDI-TRE to the systemic circulation. Gas exchange was not negatively affected. CO=cardiac output; HR=heart rate; SaO₂=arterial oxygen saturation; SvO₂=central venous oxygen saturation. Data are given as mean value±SEM.

FIG. 3 shows areas under the curve for changes in pulmonary vascular resistance (PVR) calculated for an observation period of 120 minutes after inhalation treprostinil using a metered dose inhaler. PVR was markedly lowered by treprostinil inhalation. The increased pulmonary vasodilation over time with the two highest doses mainly relies on the more sustained effect over time. Data are shown as mean value±95% confidence intervals.

FIG. 4 demonstrates Ventilation-perfusion matching measured with the multiple inert gas elimination technique. Five patients (30 µg TRE, n=2; 45 µg TRE, n=1; 60 µg TRE, n=2) with pre-existing gas exchange problems were investigated for changes in ventilation-perfusion ratios. All patients had significant shunt flow at baseline. Shunt-flow and low V/Q areas were not significantly changed by nitric oxide (NO) inhalation or treprostinil inhalation using a metered dose inhaler (MDI-TRE). MDI-TRE applied at high treprostinil concentrations did not negatively affect ventilation-perfusion matching and gas-exchange. Data are given as mean value±95% confidence intervals.

FIG. 5 presents response of pulmonary vascular resistance (PVR) to inhaled treprostinil vs. iloprost—period effects. a)

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First inhalation with treprostinil (n=22) vs. first inhalation with iloprost (n=22); b) second inhalation with treprostinil (n=22) vs. second inhalation with iloprost (n=22). The PVR decrease with treprostinil was delayed and prolonged, compared to iloprost. Due to carryover effects from the first period, in the second period, the effects of both drugs appeared shortened. Data are shown as percent of baseline values (mean value±95% confidence interval).

FIG. 6 presents response of PVR and systemic arterial pressure (SAP) to inhalation of treprostinil vs. iloprost dose effects. a) Inhalation of 7.5 µg iloprost (in 6 min) vs. 7.5 µg treprostinil (6 min) (n=14, in a randomized order). b) Inhalation of 7.5 µg iloprost (6 min) vs. 15 µg treprostinil (6 min) (n=14, in randomized order). c) Inhalation of 7.5 µg iloprost (6 min) vs. 15 µg treprostinil (3 min) (n=16, in randomized order). Data are shown as percent of baseline values (mean±95% confidence interval). Iloprost, filled circles; Treprostinil, open triangles.

FIG. 7 presents hemodynamic response to inhalation of treprostinil vs. iloprost. Data from n=44 patients, who inhaled both drugs in randomized order, shown as percent of baseline values (mean value±95% confidence interval). PVR, pulmonary vascular resistance; PAP, mean pulmonary arterial pressure; SAP, mean systemic arterial pressure; CO, cardiac output.

FIG. 8 presents pharmacodynamics after treprostinil inhalation vs. placebo. Placebo or treprostinil in doses of 30 µg, 60 µg or 90 µg were inhaled (means±95% confidence intervals). Maximal decrease of PVR was comparable for all doses. The duration of pulmonary vasodilation (PVR-decrease) appeared to be dose dependent. PVR, pulmonary vascular resistance; PAP, mean pulmonary arterial pressure; SAP, mean systemic arterial pressure; CO, cardiac output; SaO₂, arterial oxygen saturation; SvO₂, mixed venous oxygen saturation.

FIG. 9 presents Areas Between the placebo and the treprostinil Curves (ABC). ABCs were calculated for a 3-hour period after inhalation of TRE or placebo from the relative changes of hemodynamic parameters (means±95% confidence intervals). PVR, pulmonary vascular resistance; PAP, mean pulmonary arterial pressure; SAP, mean systemic arterial pressure; SVR, systemic vascular resistance.

FIG. 10 presents hemodynamic responses to the inhalation of 15 µg treprostinil. The inhalation time by increasing treprostinil concentration. A pulse of aerosol was generated every 6 seconds. TRE aerosol was inhaled in concentrations of 100 µg/ml (18 pulses; n=6), 200 µg/ml (9 pulses; n=6), 600 µg/ml (3 pulses; n=21), 1000 µg/ml (2 pulses; n=7) and 2000 µg/ml (1 pulse; n=8). Placebo data correspond to FIG. 8. Data are shown as means±95% confidence intervals. PVR, pulmonary vascular resistance; PAP, mean pulmonary arterial pressure; SAP, mean systemic arterial pressure; CO, cardiac output.

FIG. 11 presents areas between the placebo curve and the responses to 15 µg treprostinil applied at increasing concentrations to minimize inhalation time. Mean±SEM of relative changes of hemodynamic parameters (observation time 120 min). PAP, pulmonary arterial pressure, SAP, systemic arterial pressure, PVR, pulmonary vascular resistance, CO, cardiac output, SaO₂, systemic arterial oxygen saturation, SvO₂, pulmonary arterial oxygen saturation.

FIG. 12 presents pharmacokinetics of treprostinil after a single inhalation. Treprostinil plasma levels after inhalation of 30 µg, 60 µg, 90 µg or 120 µg treprostinil (6 min inhalation period; experiments correspond to those shown in FIGS. 8 and 9). Data with error bars represent mean values±SEM.

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DETAILED DESCRIPTION OF THE INVENTION

Unless otherwise specified, the term “a” or “an” used herein shall mean “one or more.”

The present application incorporates herein by reference in its entirety Voswinckel R, et al. J. Am. Coll. Cardiol. 2006; 48:1672-1681.

The inventors discovered that a therapeutically effective dose of treprostinil can be administered in a few single inhalations using a compact inhalation device, such as a metered dose inhaler. Furthermore, the inventors discovered that such administering does not cause significant side effects, especially no significant side effects related to systemic blood pressure and circulation as well as no gas exchange deteriorations or disruptions.

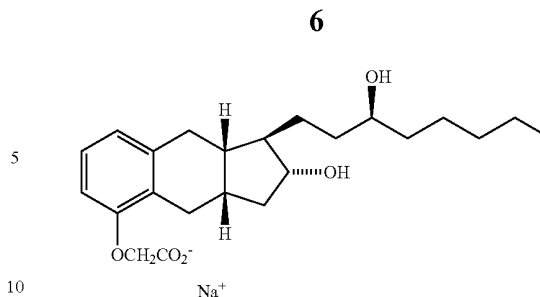
Accordingly, one embodiment of the invention is a method of delivering to a subject in need thereof, such as a human being, a therapeutically effective amount of treprostinil comprising administering to the subject a formulation comprising a therapeutically effective amount of treprostinil, its derivative or a pharmaceutically acceptable salt thereof using a metered dose inhaler. Treprostinil can be administered via a metered dose inhaler to a subject affected with a condition or disease, which can be treated by treprostinil, such as asthma, pulmonary hypertension, peripheral vascular disease or pulmonary fibrosis.

Another embodiment of the invention is a method for treating pulmonary hypertension, comprising administering to a subject in need thereof, such as a human being, treprostinil or its derivative, or a pharmaceutically acceptable salt using a metered dose inhaler.

Treprostinil, or 9-deoxy-2',9- α -methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)-13,14-dihydro-prostaglandin F₁, is a prostacyclin analogue, first described in U.S. Pat. No. 4,306,075. U.S. Pat. No. 5,153,222 describes use of treprostinil for treatment of pulmonary hypertension. Treprostinil is approved for the intravenous as well as subcutaneous route, the latter avoiding septic events associated with continuous intravenous catheters. U.S. Pat. Nos. 6,521,212 and 6,756,033 describe administration of treprostinil by inhalation for treatment of pulmonary hypertension, peripheral vascular disease and other diseases and conditions. U.S. Pat. No. 6,803,386 discloses administration of treprostinil for treating cancer such as lung, liver, brain, pancreatic, kidney, prostate, breast, colon and head-neck cancer. US patent application publication No. 2005/0165111 discloses treprostinil treatment of ischemic lesions. U.S. Pat. No. 7,199,157 discloses that treprostinil treatment improves kidney functions. US patent application publication No. 2005/0282903 discloses treprostinil treatment of neuropathic foot ulcers. U.S. provisional application No. 60/900,320 filed Feb. 9, 2007, discloses treprostinil treatment of pulmonary fibrosis.

The term “acid derivative” is used herein to describe C1-4 alkyl esters and amides, including amides wherein the nitrogen is optionally substituted by one or two C1-4 alkyl groups.

The present invention also encompasses methods of using Treprostinil or its derivatives, or pharmaceutically acceptable salts thereof. In one embodiment, a method uses Treprostinil sodium, currently marketed under the trade name of REMODULIN®. The FDA has approved Treprostinil sodium for the treatment of pulmonary arterial hypertension by injection of dose concentrations of 1.0 mg/mL, 2.5 mg/mL, 5.0 mg/mL and 10.0 mg/mL. The chemical structure formula for Treprostinil sodium is:



Treprostinil sodium is sometimes designated by the chemical names: (a) [(1R,2R,3aS,9aS)-2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]acetic acid; or (b) 9-deoxy-2',9- α -methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)-13,14-dihydro-prostaglandin F₁. Treprostinil sodium is also known as: UT-15; LRX-15; 15AU81; UNIPROST™; BW A15AU; and U-62,840. The molecular weight of Treprostinil sodium is 390.52, and its empirical formula is C₂₃H₃₄O₅.

In certain embodiments, treprostinil can be administered in combination with one or more additional active agents. In some embodiments, such one or more additional active agents can be also administered together with treprostinil using a metered dose inhaler. Yet in some embodiments, such one or more additional active agents can be administered separately from treprostinil. Particular additional active agents that can be administered in combination with treprostinil may depend on a particular disease or condition for treatment or prevention of which treprostinil is administered. In some cases, the additional active agent can be a cardiovascular agent such as a calcium channel blocker, a phosphodiesterase inhibitor, an endothelial antagonist, or an antiplatelet agent.

The present invention extends to methods of using physiologically acceptable salts of Treprostinil, as well as non-physiologically acceptable salts of Treprostinil that may be used in the preparation of the pharmacologically active compounds of the invention.

The term “pharmaceutically acceptable salt” refers to a salt of Treprostinil with an inorganic base, organic base, inorganic acid, organic acid, or basic or acidic amino acid. Salts of inorganic bases can be, for example, salts of alkali metals such as sodium or potassium; alkaline earth metals such as calcium and magnesium or aluminum; and ammonia. Salts of organic bases can be, for example, salts trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, and triethanolamine. Salts of inorganic acids can be, for example, salts of hydrochloric acid, hydroboric acid, nitric acid, sulfuric acid, and phosphoric acid. Salts of organic acids can be, for example, salts of formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, lactic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, and p-toluenesulfonic acid. Salts of basic amino acids can be, for example, salts of arginine, lysine and ornithine. Salts of acidic amino acids can include, for example, salts of aspartic acid and glutamic acid. Quaternary ammonium salts can be formed, for example, by reaction with lower alkyl halides, such as methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides, with dialkyl sulfates, with long chain halides, such as decyl, lauryl, myristyl, and stearyl chlorides, bromides, and iodides, and with aralkyl halides, such as benzyl and phenethyl bromides.

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Preferred pharmaceutically acceptable salts are disclosed, for example, in US patent application publication No. 20050085540.

Treprostinil can be administered by inhalation, which in the present context refers to the delivery of the active ingredient or a combination of active ingredients through a respiratory passage, wherein the subject in need of the active ingredient(s) through the subject's airways, such as the subject's nose or mouth.

A metered dose inhaler in the present context means a device capable of delivering a metered or bolus dose of respiratory drug, such as treprostinil, to the lungs. One example of the inhalation device can be a pressurized metered dose inhaler, a device which produces the aerosol clouds for inhalation from solutions and/or suspensions of respiratory drugs in chlorofluorocarbon (CFC) and/or hydrofluoroalkane (HFA) solutions.

The inhalation device can be also a dry powder inhaler. In such case, the respiratory drug is inhaled in solid formulation, usually in the form of a powder with particle size less than 10 micrometers in diameter or less than 5 micrometers in diameter.

The metered dose inhaler can be a soft mist inhaler (SMI), in which the aerosol cloud containing a respiratory drug can be generated by passing a solution containing the respiratory drug through a nozzle or series of nozzles. The aerosol generation can be achieved in SMI, for example, by mechanical, electromechanical or thermomechanical process. Examples of soft mist inhalers include the Respimat® Inhaler (Boeringer Ingelheim GmbH), the AERx® Inhaler (Aradigm Corp.), the Mystic™ Inhaler (Ventaira Pharmaceuticals, Inc) and the Aira™ Inhaler (Chrysalis Technologies Incorporated). For a review of soft mist inhaler technology, see e.g. M. Hindle, The Drug Delivery Companies Report, Autumn/Winter 2004, pp. 31-34. The aerosol for SMI can be generated from a solution of the respiratory drug further containing pharmaceutically acceptable excipients. In the present case, the respiratory drug is treprostinil, its derivative or a pharmaceutically acceptable salt thereof, which can be formulated in SMI is as a solution. The solution can be, for example, a solution of treprostinil in water, ethanol or a mixture thereof. Preferably, the diameter of the treprostinil-containing aerosol particles is less than about 10 microns, or less than about 5 microns, or less than about 4 microns.

Treprostinil concentration in an aerosolable formulation, such as a solution, used in a metered dose inhaler can range from about 500 µg/ml to about 2500 µg/ml, or from about 800 µg/ml to about 2200 µg/ml, or from about 1000 µg/ml to about 2000 µg/ml.

The dose of treprostinil that can be administered using a metered dose inhaler in a single event can be from about 15 µg to about 100 µg or from about 15 µg to about 90 µg or from about 30 µg to about 90 µg or from about 30 µg to about 60 µg.

Administering of treprostinil in a single event can be carried out in a limited number of breaths by a patient. For example, treprostinil can be administered in 20 breaths or less, or in 10 breaths or less, or than 5 breaths or less. Preferably, treprostinil is administered in 3, 2 or 1 breaths.

The total time of a single administering event can be less than 5 minutes, or less than 1 minute, or less than 30 seconds.

Treprostinil can be administered a single time per day or several times per day.

In some embodiments, the method of treatment of pulmonary hypertension can further comprise administering at

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least one supplementary agent selected from the group consisting of sildenafil, tadalafil, calcium channel blockers (diltiazem, amlodipine, nifedipine), bosentan, sitaxsentan, ambrisentan, and pharmaceutically acceptable salts thereof. In some embodiments, the supplementary agents can be included in the treprostinil formulation and, thus, can be administered simultaneously with treprostinil using a metered dose inhaler. In some embodiments, the supplementary agents can be administered separately from treprostinil. In some embodiments, the application of intravenous prostacyclin (flolan), intravenous iloprost or intravenous or subcutaneous treprostinil can be administered in addition to treprostinil administered via inhalation using a metered dose inhaler.

The present invention also provides a kit that includes a metered dose inhaler containing a pharmaceutical formulation comprising treprostinil or its derivative, or a pharmaceutically acceptable salt thereof. Such a kit can further include instructions on how to use the metered dose inhaler for inhaling treprostinil. Such instructions can include, for example, information on how to coordinate patient's breathing, and actuation of the inhaler. The kit can be used by a subject, such as human being, affected with a disease or condition that can be treated by treprostinil, such as asthma, pulmonary hypertension, peripheral vascular disease or pulmonary fibrosis.

In some cases, the kit is a kit for treating pulmonary hypertension, that includes (i) a metered dose inhaler containing a pharmaceutical formulation comprising treprostinil or its derivative, or a pharmaceutically acceptable salt thereof; and (ii) instructions for use of the metered dose inhaler containing treprostinil in treating pulmonary hypertension.

As used herein, the phrase "instructions for use" shall mean any FDA-mandated labeling, instructions, or package inserts that relate to the administration of Treprostinil or its derivatives, or pharmaceutically acceptable salts thereof, for treatment of pulmonary hypertension by inhalation. For example, instructions for use may include, but are not limited to, indications for pulmonary hypertension, identification of specific symptoms associated with pulmonary hypertension, that can be ameliorated by Treprostinil, recommended dosage amounts for subjects suffering from pulmonary hypertension and instructions on coordination of individual's breathing and actuation of the metered dose inhaler.

The present invention can be illustrated in more detail by the following example, however, it should be understood that the present invention is not limited thereto.

EXAMPLE 1

Open Label Study Upon Acute Safety, Tolerability and Hemodynamic Effects of Inhaled Treprostinil Delivered in Seconds

A study was conducted of acute vasodilator challenge during right heart catheter investigation to determine the safety, tolerability and pulmonary vasodilatory potency of inhaled treprostinil applied in seconds by a soft mist inhaler (SMI-TRE). The study produced evidence for a long lasting favourable effect of SMI-TRE on pulmonary hemodynamics in absence of systemic side effects and gas exchange disruptions.

SUMMARY

Inhaled nitric oxide (20 ppm; n=45) and inhaled treprostinil sodium (TRE; n=41) or placebo (n=4) were applied

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once during right heart catheter investigation. TRE was delivered in 2 breaths (1000 µg/ml aerosol concentration; 30 µg dose; n=12), 3 breaths (1000 µg/ml; 45 µg; n=9) or 2 breaths (2000 µg/ml; 60 µg; n=20) from a Respimat® SMI. Pulmonary hemodynamics and blood gases were measured at defined time points, observation time following TRE application was 120 minutes. TRE doses of 30 µg, 45 µg and 60 µg reduced pulmonary vascular resistance (PVR) to 84.4±8.7%, 71.4±17.5% and 77.5±7.2% of baseline values, respectively (mean±95% confidence interval). The 120 minute area under the curve for PVR for placebo, 30 µg, 45 µg and 60 µg TRE was 1230±1310, -870±940, -2450±2070 and -2000±900 min %, respectively. Reduction of PVR by a single inhalation of the two higher doses outlasted the observation period of 120 minutes. Reduction of systemic vascular resistance and pressure was negligible, showing a high pulmonary selectivity for SMI-TRE. Intrapulmonary selectivity was also provided by SMI-TRE as ventilation/perfusion matching, assessed by the multiple inert gas elimination technique in 5 patients with gas exchange problems, was not significantly different after SMI-TRE compared to inhaled nitric oxide or no treatment. No significant side effects were observed.

Conclusions: The acute application of inhaled treprostinil with a metered dose inhaler in 2-3 breaths was safe, well tolerated and induced a strong and sustained pulmonary selective vasodilation.

Methods and Patients

A total number of 45 patients with moderate to severe precapillary pulmonary hypertension were enrolled. Patient characteristics were: female to male ratio (f/m)=29/16, age 59±2.3 years, pulmonary artery pressure (PAP) 45±1.8 mmHg, pulmonary vascular resistance (PVR) 743±52 dynes·s·cm⁻⁵, pulmonary artery wedge pressure (PAWP) 8.6±0.5 mmHg, central venous pressure (CVP) 6.4±0.7 mmHg, cardiac output (CO) 4.5±0.21/min, central venous oxygen saturation (SvO2) 62.3±1.2 mmHg (mean±Standard Error of the Mean). Disease etiologies were idiopathic PAH (iPAH) (n=13), PAH other (n=11), chronic thromboembolic pulmonary hypertension (CTEPH) (n=17) and pulmonary fibrosis (n=4). Table 1 presents the patient characteristics of the different groups.

TABLE 1

Patient characteristics of the different treatment groups. Data are given as mean ± Standard Error of the Mean (SEM). PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; CO = cardiac output; SAP = systemic arterial pressure; SaO2 = arterial oxygen saturation; SvO2 = central venous oxygen saturation.				
	Placebo (n = 4)	30 µg TRE (n = 12)	45 µg TRE (n = 9)	60 µg TRE (n = 20)
Age [years]	61 ± 8	53.9 ± 3.9	54.2 ± 5.7	65.5 ± 3.1
PAP [mmHg]	49.5 ± 10.1	45 ± 3.1	54.3 ± 2.8	39.7 ± 2.0
PVR [Dynes]	896 ± 163	597 ± 53.9	1049 ± 107	663 ± 81
CO [l/min]	4.46 ± 0.9	5.2 ± 0.4	3.9 ± 0.4	4.4 ± 0.3
SAP [mmHg]	98 ± 8.1	90.1 ± 3.2	82.8 ± 3.9	86.1 ± 2.0
SaO2 [%]	85.3 ± 4.5	90.0 ± 1.1	89.6 ± 1.1	90.6 ± 0.5
SvO2 [%]	57.5 ± 3.9	66.0 ± 1.6	59.1 ± 3.4	62.5 ± 1.6

Baseline values were determined 20-30 minutes after placement of the catheter. Heart rate, pulmonary and systemic blood pressure and cardiac output were measured and blood gases were taken during each pharmacological intervention at defined time points. Pharmacological interventions included the inhalation of 20 ppm nitric oxide (NO) after evaluation of baseline parameters (n=45) and the

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consecutive inhalation of placebo (n=4), 30 µg SMI-TRE (n=12), 45 µg SMI-TRE (n=9) or 60 µg (n=20) SMI-TRE. Placebo and treprostinil was applied with the Respimat® SMI. For filling of this device with treprostinil sodium, the placebo solution was withdrawn from the device with a syringe and treprostinil solution was injected into the device under sterile conditions. Aerosol quality was controlled before and after refilling of the SMI devices by laser diffractometry, see e.g. Gessler T., Schmehl T., Hoeper M. M., Rose F., Ghofrani H. A., Olschewski H. et al. Ultrasonic versus jet nebulization of iloprost in severe pulmonary hypertension. Eur. Respir. J. 2001; 17:14-19 incorporated herein in its entirety. The aerosol sizes before (placebo) and after filling (treprostinil) were unchanged. The aerosol particles mass median aerodynamic diameter of treprostinil-aerosol was 4-5 µm, which can be at the upper limit for alveolar deposition. The aerosol volume delivered by one cycle from the SMI was 15 µl. The solution used for aerosol generation was prepared from treprostinil sodium salt using a standard protocol. The SMI was either filled with a concentration of 1000 µg/ml treprostinil sodium (one aerosol puff=15 µg TRE) or with 2000 µg/ml (one puff=30 µg TRE). The different doses were applied as 2 puffs 1000 µg/ml (30 µg), 3 puffs 1000 µg/ml (45 µg) and 2 puffs 2000 µg/ml (60 µg). The placebo was inhaled as 2 puffs from a placebo-SMI. Hemodynamics and gas-exchange parameters were recorded for 120 minutes after TRE inhalation. This study used the Respimat® device, because the implemented "soft mist" technology was well suited for the deposition of such highly active drugs like prostanoids.

The impact of SMI-TRE on ventilation-perfusion matching was assessed in five patients (30 µg TRE, n=2; 45 µg TRE, n=1; 60 µg TRE, n=2) with pre-existing gas exchange problems by use of the multiple inert gas elimination technique (MIGET), see e.g. Wagner P D, Saltzman H A, West J B. Measurement of continuous distributions of ventilation-perfusion ratios: theory. J Appl Physiol. 1974; 36:588-99; Ghofrani H A, Wiedemann R, Rose F, Schemmuly R T, Olschewski H, Weissmann N et al. Sildenafil for treatment of lung fibrosis and pulmonary hypertension: a randomised controlled trial. Lancet. 2002; 360:895-900, both incorporated herein in their entirety.

Statistics:

Mean values, standard deviation, standard error of the mean and 95% confidence intervals were calculated. Statistical analysis was done by use of a paired t-test.

Results:

The inhalation of treprostinil sodium from the metered dose inhaler (SMI-TRE) was well tolerated, only mild and transient cough for a maximum of one minute was reported. No systemic side effects like headache, flush, nausea or dizziness were observed.

Two to three breaths of SMI-TRE induced a strong pulmonary vasodilation that outlasted the observation time of 120 minutes (45 and 60 µg). The lower dose of 30 µg TRE induced a somewhat shorter effect on pulmonary vascular resistance; however, the maximal pulmonary vasodilation was comparable. In contrast, placebo inhalation did not induce pulmonary vasodilation. In fact a slight increase in PVR over the time of the right heart catheter investigation could be recorded following placebo inhalation (FIG. 1). The effect of SMI-TRE on systemic vascular resistance and pressure was very small and not clinically significant. Cardiac output was significantly increased over the whole observation period, whereas heart rate was rather unchanged. Gas exchange was not influenced by SMI-TRE

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(FIG. 2). The maximal changes in hemodynamic and gas-exchange parameters compared to baseline values are depicted in Table 2.

TABLE 2

Extremes of the relative changes of hemodynamic and gas exchange parameters compared to baseline after inhalation of Placebo (n = 4), 30 µg treprostinil (n = 12), 45 µg treprostinil (n = 9) and 60 µg treprostinil (n = 20). Highest (max) and lowest (min) values during the observation period are shown. Data are given as percent of baseline values (mean ± SEM). PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance; CO = cardiac output; SAP = systemic arterial pressure; HR = heart rate; SaO ₂ = arterial oxygen saturation; SvO ₂ = central venous oxygen saturation.				
	Placebo	30 µg TRE	45 µg TRE	60 µg TRE
PAP (min)	99.4 ± 3.0	83.4 ± 3.2	77.6 ± 6.8	79.5 ± 2.4
PVR (min)	101.4 ± 1.9	84.4 ± 4.4	71.4 ± 8.9	77.5 ± 3.7
CO (max)	99.7 ± 1.1	108.8 ± 3.8	108.6 ± 5.6	103.8 ± 2.0
SVR (min)	104.3 ± 4.3	97.7 ± 4.2	92 ± 3.9	91.3 ± 2.1
SAP (min)	102.7 ± 1.7	97.3 ± 1.9	96.1 ± 1.5	93.6 ± 2.9
HR (max)	105 ± 2.1	106.1 ± 2.9	99.1 ± 2.4	101.1 ± 0.9
SaO ₂ (min)	98.2 ± 0.4	101 ± 0.3	94.4 ± 1.8	95.8 ± 0.9
SvO ₂ (max)	104.5 ± 1.4	102.4 ± 1.3	104.5 ± 4.4	102 ± 1.0

The areas under the curve for PVR were calculated for placebo and the different SMI-TRE doses over the 120 minute observation period (FIG. 3). A dose effect of SMI-TRE with a trend to a more sustained effect with the two highest doses could be observed.

The inhalation of a highly concentrated aerosol can be in theory prone to disturbances of gas exchange because the deposition of even small amounts of aerosol may deliver high doses locally and thereby antagonize the hypoxic pulmonary vasoconstriction in poorly ventilated areas. This would then lead to increased shunt flow or increase of low ventilation/perfusion (V/Q) areas. This question was addressed in five patients with the multiple inert gas elimination technique (MIGET), the gold-standard for intrapulmonary V/Q ratio determination. The MIGET patients were selected for pre-existing gas exchange limitations. Characteristics of these patients were: PAP 54.6±3.2 mmHg, PVR 892±88 dynes, SaO₂ 91.7±0.5%, SvO₂ 65.2±1.8%. Etiologies were iPAH (n=1), CTEPH (n=3), pulmonary fibrosis (n=1). The maximal relative reduction of SaO₂ after inhalation of SMI-TRE in these patients was -3.8±1.5% compared to baseline values. Shunt flow at baseline, NO-inhalation and 60 minutes after SMI-TRE was 6.4±4.3%, 5.4±3.0% and 8.3±3.4%, respectively (mean±95% confidence interval; FIG. 4).

No significant increase in low V/Q areas or shunt fraction after inhalation of SMI-TRE was observed, in fact the distribution of perfusion was not different to that at baseline and during nitric oxide inhalation. This proves an excellent intrapulmonary selectivity of SMI-TRE, which is also reflected by unchanged arterial oxygen saturation.

Conclusion:

Treprostinil is tolerated at high doses with no systemic side effects. The application of an effective amount of treprostinil in only few or even one single breath was achieved with a highly concentrated treprostinil sodium solution. Treprostinil can be applied by a metered dose inhaler, such as RespiMat® soft mist inhaler.

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EXAMPLE 2

Investigation of the Effects of Inhaled Treprostinil on Pulmonary Hemodynamics and Gas Exchange in Severe Pulmonary Hypertension

This study investigated the effects of inhaled treprostinil on pulmonary vascular resistance in severe pulmonary hypertension and addressed systemic effects and gas exchange as well as tolerability and efficacy of high doses of treprostinil given in short time. A total of 123 patients with a mean pulmonary artery pressure of about 50 mmHg were investigated in three separate randomized studies. Inhaled treprostinil exerted potent sustained pulmonary vasodilation with excellent tolerability and could be safely applied in a few breaths or even one breath.

Summary:

Three different studies were conducted on a total of 123 patients by means of right heart catheterization: i) a randomized crossover-design study (44 patients), ii) a dose escalation study (31 patients) and iii) a study of reduction of inhalation time while keeping the dose fixed (48 patients). The primary endpoint was the change in pulmonary vascular resistance (PVR).

The mean pulmonary artery pressure of the enrolled patients was about 50 mmHg. Hemodynamics and patient characteristics were similar in all studies. In study i) TRE and Iloprost (ILO), at an inhaled dose of 7.5 µg, displayed comparable PVR decrease, with a significantly different time course (p<0.001), TRE exhibiting a more sustained effect on PVR (p<0.0001) and less systemic side effects. In study ii) placebo, 30 µg, 60 µg, 90 µg or 120 µg TRE were applied with drug effects being observed for 3 hours after inhalation. A near-maximal acute PVR decrease was observed at 30 µg TRE. In study iii) TRE was inhaled with a pulsed ultrasonic nebulizer, mimicking a metered dose inhaler. 15 µg TRE was inhaled with 18 pulses (TRE concentration 100 µg/ml), 9 pulses (200 µg/ml), 3 pulses (600 µg/ml), 2 pulses (1000 µg/ml) or 1 pulse (2000 µg/ml), each mode achieving comparable, sustained pulmonary vasodilation.

Inhaled treprostinil exerts sustained pulmonary vasodilation with excellent tolerability at doses, which may be inhaled in a few or even one breath. Inhaled treprostinil is advantageous to inhaled iloprost in terms of duration of effect and systemic side effects. Inhaled treprostinil is well tolerated in concentrations up to 2000 mg/ml (bringing down inhalation time to a single breath) and in high doses (up to 90 µg).

Methods:

All inhalations were performed with the OPTINEB® ultrasonic nebulizer (Nebutech, Elsenfeld, Germany).

Study i) was a randomized, open-label, single-blind crossover study. The primary objective was to compare the acute hemodynamic effects and the systemic side effects of inhaled treprostinil with inhaled iloprost at comparable doses. A total number of 44 patients with moderate to severe precapillary pulmonary hypertension were enrolled. Patient characteristics and hemodynamic as well as gas exchange parameters are outlined in Table 3.

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TABLE 3

Patient characteristics, hemodynamic parameters and gas exchange values at baseline, before challenge with inhalative prostanoids.							
Group 1 corresponds to study i); randomized crossover study comparing inhaled iloprost (ILO) and inhaled treprostinil (TRE). a = 7.5 g ILO vs. 7.5 µg TRE, b = 7.5 g ILO vs. 15 µg TRE (6 min inhalation time), c = 7.5 g ILO vs. 15 µg TRE (3 min inhalation time). Group 2 corresponds to study ii); evaluation of maximal tolerated dose of TRE. a = placebo inhalation, b = 30 µg TRE, c = 60 µg TRE, d = 90 µg TRE, e = 120 µg TRE. Group 3 corresponds to study iii); reduction of inhalation time by increase of TRE concentration, aiming at a total inhaled dose of 15 µg. a = 18 pulses of 100 µg/ml TRE, b = 9 pulses of 200 µg/ml TRE, c = 3 pulses of 600 µg/ml TRE, d = 2 pulses of 1000 µg/ml TRE, e = 1 pulse 2000 µg/ml TRE. Etiology of pulmonary hypertension was classified as idiopathic PAH (i), PAH of other causes (o), chronic thromboembolic PH (t), and pulmonary fibrosis (f).							
	N	Age	Gender f/m	Etiology i/o/t/f	PAP [mmHg]	PVR [dyn * s * cm ⁻⁵]	SAP [mmHg]
1a	14	55.1 ± 4.8	11/3	4/4/2/4	53.8 ± 3.1	911 ± 102	95.4 ± 3.6
1b	14	54.1 ± 3.3	10/4	1/6/5/2	47.4 ± 3.8	716 ± 80	90.6 ± 3.3
1c	16	56 ± 2.9	7/9	6/3/6/1	47.5 ± 4.5	777 ± 102	92 ± 4.5
2a	8	60.8 ± 4	4/4	2/2/3/1	51.9 ± 4.9	849 ± 152	95.9 ± 4.8
2b	8	52.8 ± 6.6	6/2	1/3/3/1	49 ± 4	902 ± 189	92.4 ± 2.4
2c	6	56.8 ± 5.9	4/2	0/2/2/2	44.2 ± 3.5	856 ± 123	96.3 ± 3.9
2d	6	51.2 ± 3.8	4/2	2/2/2/0	55.5 ± 4.9	940 ± 110	91.2 ± 8.1
2e	3	57.3 ± 9.1	1/2	0/1/0/2	45.3 ± 5.2	769 ± 267	99 ± 3.2
3a	6	52.7 ± 6.6	4/2	2/4/0/0	53.8 ± 6.7	928 ± 145	92.7 ± 7.9
3b	6	58.3 ± 3.5	4/2	3/1/1/1	54.2 ± 6.1	808 ± 156	94.3 ± 2.8
3c	21	57.4 ± 5.6	8/3	7/7/6/1	46.1 ± 2.5	900 ± 99	88 ± 2.8
3d	7	55.6 ± 5.8	3/4	0/4/3/0	53.1 ± 7.1	732 ± 123	91.4 ± 5.6
3e	8	59 ± 5.2	7/1	0/4/4/0	45.1 ± 3.9	733 ± 114	92.8 ± 6.8

	CVP [mmHg]	PAWP [mmHg]	CO [l/min]	SaO2 [%]	SvO2 [%]
1a	7.4 ± 1	8.0 ± 0.8	4.3 ± 0.4	93.8 ± 2	63.9 ± 2.4
1b	5.9 ± 1.4	6.4 ± 0.7	4.7 ± 0.4	92 ± 1	64.4 ± 2.3
1c	8.3 ± 1.4	8.6 ± 1.4	4.4 ± 0.5	91.4 ± 0.9	59.8 ± 2.6
2a	7.6 ± 1.4	11.1 ± 1.7	4.4 ± 0.6	89.6 ± 2.8	60.1 ± 2.8
2b	4.8 ± 1.1	7.2 ± 1.3	4.0 ± 0.4	92.4 ± 2.4	62.5 ± 1.7
2c	5 ± 1.1	6 ± 1	3.8 ± 0.3	92.8 ± 1.5	63.6 ± 1.8
2d	11.2 ± 1.2	10 ± 0.7	3.9 ± 0.4	92 ± 1.9	62 ± 5.8
2e	5 ± 2.1	9 ± 0.6	4.5 ± 0.6	94.2 ± 1.3	66.3 ± 1.5
3a	8.7 ± 2.7	8.8 ± 1.3	4.2 ± 0.6	90.4 ± 2.8	64.8 ± 4.3
3b	7 ± 1.4	10 ± 1.3	5 ± 0.7	91.9 ± 0.7	63.5 ± 2.9
3c	9 ± 1.4	9.2 ± 0.5	3.7 ± 0.3	91.7 ± 0.5	59.7 ± 2
3d	7.9 ± 3.1	8.6 ± 1.3	5 ± 0.4	90.7 ± 1.4	61.3 ± 3.7
3e	4.6 ± 0.8	8.1 ± 1.1	4.3 ± 0.2	90.7 ± 0.8	66.3 ± 2.8

Each patient inhaled both iloprost and treprostinil on the same day during right heart catheter investigation; the drugs were administered consecutively with a one hour interval between the drug applications. One half of the study patients initially inhaled treprostinil and then inhaled iloprost (n=22), while the other half initially inhaled iloprost and then inhaled treprostinil (n=22). Patients were randomized to one of the two groups and blinded as to the study drugs. Drug effects were monitored for 60 minutes after each inhalation. Iloprost was inhaled at 4 µg/ml (6 min inhalation time; n=44) and treprostinil was inhaled at a concentration of 4 µg/ml (6 min inhalation; n=14), 8 µg/ml (6 min inhalation; n=14) or 16 µg/ml (3 min inhalation; n=16). Based on previous biophysical characterization of the ultrasonic device with iloprost- and treprostinil-solution, this corresponds to a total inhaled dose of 7.5 µg iloprost and treprostinil (4 µg/ml) and 15 µg treprostinil (8 µg/ml and 16 µg/ml), respectively.

Study ii) was a randomized, open-label, single blind, placebo controlled study. The primary objectives were to describe the pharmacodynamic and pharmacokinetic effects of inhaled treprostinil at a well tolerated dose (30 µg) and to explore the highest tolerated single dose. A total number of 31 patients inhaled either placebo or treprostinil; each patient received one inhalation. The first 16 patients were randomized to 30 µg TRE (16 µg/ml, n=8) or placebo (stock

solution in a concentration corresponding to TRE 16 µg/ml). Subsequent patients received 60 µg TRE (32 µg/ml; n=6), 90 µg TRE (48 µg/ml; n=6) and 120 µg TRE (64 µg/ml; n=3). Inhalation time was 6 minutes in all groups. Hemodynamics and gas-exchange as well as arterial treprostinil concentrations were recorded for 180 minutes.

Study iii) was a randomized, open-label, single blind study. The primary objective was to explore the shortest possible inhalation time for a 15 µg dose of inhaled treprostinil. A total of 48 patients inhaled one dose of TRE during right heart catheter investigation. The drug was applied in 18, 9, 3, 2 or 1 breaths. The aerosol was generated by a pulsed ultrasonic nebulizer (OPTINEB®, Nebutech, Elsenfeld, Germany) in cycles consisting of 2 seconds aerosol production (pulse) and 4 seconds pause. The device included an opto-acoustical trigger for the patient to synchronize the inspiration to the end of the aerosol pulse, thereby providing exact dosage. The TRE dose of 15 µg was either generated during 18 cycles (OPTINEB® filled with 100 µg/ml TRE, n=6), 9 cycles (200 µg/ml TRE, n=6), 3 cycles (600 µg/ml TRE, n=21), 2 cycles (1000 µg/ml TRE, n=7) or 1 cycle (2000 µg/ml TRE, n=8). Hemodynamics and gas exchange were recorded for 120-180 minutes.

Treprostinil plasma concentrations were assessed in study ii) at 10, 15, 30, 60 and 120 minutes after inhalation.

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Treprostinil quantification was done by Alta Analytical Laboratory (El Dorado Hills, Calif., USA) with a validated liquid chromatography atmospheric-pressure ionization tandem mass spectrometry as previously described Wade M., et al. *J. Clin. Pharmacol.* 2004; 44:503-9. Mixed venous blood was drawn at the depicted time points (FIG. 11) after inhalation, centrifuged and the plasma frozen at -80°C . until temperature controlled shipping on dry ice.

Statistics:

For statistical analysis of study i) the repeated PVR measurements after inhaled iloprost and treprostinil were subjected to a three-factorial analysis of variance (ANOVA; factors: time (A), drug (B), treprostinil concentration (C)) to avoid multiple testing. The time to maximum PVR decrease after inhalation of iloprost versus treprostinil was compared by paired t-test. Area under the curve (AUC) was calculated from start of inhalation until 60 min after inhalation. Means, standard error of the mean (SEM) and 95% confidence intervals were calculated. For study ii) and iii) areas between curves (ABC) were calculated between placebo inhalation (study ii) and the respective treprostinil inhalation until 180 min (study ii) and 120 min (study iii) after end of inhalation.

Results:

The inhalation of iloprost as well as treprostinil in study i) resulted in a rapid decrease in PVR and PAP (FIG. 5-7). No significant differences were observed for the areas under the curve (AUC) of PVR decrease after inhalation of 7.5 μg TRE in 6 minutes (AUC $-12.6\pm 7.0\%$), 15 μg TRE in 6 minutes (AUC $-13.3\pm 3.2\%$) and 15 μg TRE in 3 minutes (AUC $-13.6\pm 4.3\%$). The AUC for PVR after the inhalation of 7.5 μg iloprost in 6 minutes was $7.7\pm 3.7\%$ (mean \pm 95% confidence interval). An overview of the pooled data of treprostinil inhalation as compared to iloprost inhalation is given in FIG. 7. The maximum effect of iloprost and treprostinil on PVR was comparable but this effect was reached significantly later after treprostinil inhalation (18 ± 2 min) compared to iloprost (8 ± 1 min; mean \pm SEM, $p<0.0001$) and lasted considerably longer (after 60 min, PVR values in the treprostinil group had not yet returned to baseline). The increase in cardiac output was less acute but prolonged after treprostinil inhalation. Systemic arterial pressure (SAP) was unaffected by treprostinil inhalation, whereas a transient decrease was observed after iloprost inhalation. Iloprost and treprostinil did not affect gas exchange. Three-factorial ANOVA for PVR demonstrated a significant difference between repeated measurements after inhalation ($p_{(A)}<0.0001$), no significant difference between drugs ($p_{(B)}=0.1$), no difference between treprostinil concentrations ($p_{(C)}=0.74$) and a significant drug \times time interaction ($p_{(A\times B)}<0.0001$). This translates into a significant effect of both drugs on PVR with comparable drug potency but a prolonged drug effect of treprostinil compared to iloprost.

In this study the occasionally observed mild side effects of iloprost inhalation at the given dose (transient flush, headache) were not observed with inhaled treprostinil. Bad taste was reported by most of the patients after inhalation of TRE. This was later found to be attributable to the metacresol preservative contained in the treprostinil solution.

In study ii) pharmacodynamics of inhaled placebo or treprostinil were observed for 180 minutes. Placebo inhalation was followed by a gradual increase in PVR over the entire observation time. Due to reduced patient numbers in the 120 μg TRE group (because of side effects, see below), the hemodynamic values for this group were not included in the graphs of this study (FIG. 8-9). All TRE doses lead to comparable maximal decreases of PVR to $76.5\pm 4.7\%$ (30

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μg), $73.7\pm 5.8\%$ (60 μg), $73.3\pm 4.3\%$ (90 μg) and $65.4\pm 4.1\%$ (120 μg) of baseline values. An extended duration of pulmonary vasodilation was noted, surpassing the 3 hour observation period for the 60 μg and 90 μg (and 120 μg) TRE doses, whereas in the 30 μg dose group the hemodynamic changes had just returned to baseline within this period. Even at the highest doses, TRE had only minor effects on systemic arterial pressure (FIG. 8). Cardiac output was increased to a maximum of $106.8\pm 3.2\%$ (30 μg), $122.9\pm 4.3\%$ (60 μg), $114.3\pm 4.8\%$ (90 μg) and $111.3\pm 3.9\%$ (120 μg TRE). The areas between the response curves after placebo versus TRE inhalation were calculated for PVR, PAP, SVR and SAP (FIG. 9). Areas between the curves for PVR were not significantly different for 30 μg , 60 μg and 90 μg TRE, a nearly maximal effect on PVR was already observed with 30 μg TRE. Effects on PAP and SAP were small and did not show a dose-response relationship. Gas exchange was not affected at doses up to 90 μg TRE, but arterial oxygen saturation was significantly decreased at a dose of 120 μg TRE in all 3 patients. Further dose increments were omitted due to this side effect and severe headache in one patient.

Again, bad taste of the TRE aerosol was reported by most patients. Other side effects were flushing ($n=1$; 30 μg TRE), mild transient cough ($n=3$; 60 μg TRE), mild transient bronchoconstriction that resolved after one inhalation of fenoterol ($n=1$; 30 μg TRE), moderate bronchoconstriction that resolved after one inhalation of fenoterol ($n=1$; 120 μg TRE), and severe headache ($n=1$; 120 μg TRE). The bad taste, the bronchoconstriction and the drop in SaO₂ was attributed to metacresol in the original TRE solution. With the use of a metacresol-free solution of TRE (University Hospital Giessen, Germany; produced according to the manufacturer's protocol) in the following study, these side effects did no longer occur.

Study iii) was performed with metacresol-free TRE solution, having no specific taste and smell. A total of 48 patients were enrolled. This study aimed at the reduction of inhalation time and aerosol volume needed for pulmonary drug delivery. A modified OPTINEB® inhalation device was programmed to produce a constant amount of aerosol during repeatable pulses of aerosol generation. With this device, treprostinil could be safely utilized up to a concentration of 2000 $\mu\text{g}/\text{ml}$ without considerable side effects. No relationship of number or type of side effects to TRE concentration was observed. Reported side effects were mild transient cough ($n=6$), mild headache ($n=2$) and mild jaw pain ($n=1$).

The reduction of PVR and PAP was comparable between all groups (FIG. 10). TRE inhalation reduced PVR to $76.3\pm 5.6\%$ (18 pulses, 100 $\mu\text{g}/\text{ml}$), $72.9\pm 4.9\%$ (9 pulses, 200 $\mu\text{g}/\text{ml}$), $71.2\pm 6.0\%$ (3 pulses, 600 $\mu\text{g}/\text{ml}$), $77.4\pm 4.5\%$ (2 pulses, 1000 $\mu\text{g}/\text{ml}$) and $80.3\pm 5.2\%$ (1 pulse, 2000 $\mu\text{g}/\text{ml}$). PAP was reduced to $84.2\pm 4.5\%$ (18 pulses, 100 $\mu\text{g}/\text{ml}$), $84.2\pm 4.1\%$ (9 pulses, 200 $\mu\text{g}/\text{ml}$), $81.1\pm 4.1\%$ (3 pulses, 600 $\mu\text{g}/\text{ml}$), $86\pm 4\%$ (2 pulses, 1000 $\mu\text{g}/\text{ml}$) and $88\pm 5.4\%$ (1 pulse, 2000 $\mu\text{g}/\text{ml}$). Cardiac output was moderately increased in all groups, whereas systemic arterial pressure was not significantly affected.

The areas between the curves (ABC) for changes in hemodynamic and gas-exchange parameters after inhalation of 15 μg TRE versus placebo were calculated for an observation time of 120 minutes (FIG. 11). The ABC for both PVR and PAP was comparable between all groups.

Pharmacokinetic results from study ii): Peak plasma concentrations of treprostinil were found 10-15 minutes after inhalation. Maximal treprostinil plasma concentrations (C_{max}) for the 30 μg , 60 μg , 90 μg and 120 μg doses were

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0.65±0.28 ng/ml (n=4), 1.59±0.17 ng/ml (n=4), 1.74 ng/ml (n=1) and 3.51±1.04 ng/ml (n=2), respectively (mean±SEM; FIG. 12).

Discussion:

These studies investigated whether i) the acute effects of inhaled treprostinil would be comparable to or possibly advantageous over inhaled iloprost in pulmonary hypertensive patients, ii) the inhaled prostanoid dose might be increased without substantial local or systemic side effects, and iii) if the time of inhalation, which is 6-12 minutes for iloprost, could be reduced significantly by increasing the concentration of treprostinil aerosol.

The patient population in these studies included different forms of precapillary pulmonary hypertension. All these patients had a need for therapy of pulmonary hypertension and reflected the typical population of a pulmonary hypertension center. No major differences in patient characteristics or hemodynamic baseline values existed between the different groups (table 3).

In study i) it was shown that the inhalation of treprostinil and iloprost in similar doses resulted in a comparable maximum pulmonary vasodilatory effect. However, marked differences in the response profile were noted. The onset of the pulmonary vasodilatory effect of inhaled treprostinil was delayed compared to iloprost, but lasted considerably longer, with the PVR decrease continuing beyond the one-hour observation period. Although the average dose of treprostinil was higher than the iloprost dose, no systemic effects were noted after treprostinil inhalation, whereas flush and transient SAP decrease, accompanied by more prominent cardiac output increase, occurred after iloprost inhalation. Such side effects were more prominent than in previous studies with inhaled iloprost. This may have been caused by the fact that the iloprost dose used in this study was 50% higher than the recommended single inhalation dose (5 µg) and that the preceding treprostinil inhalation may have added to the systemic side effects caused by the iloprost inhalation. Surprisingly, with TRE there was no such systemic side effect, although the average effect on PVR was as potent as with iloprost.

This study used a cross-over design in order to minimize the effects of inter-individual differences in response to prostanoids. The short observation period of 1 hour was used to avoid an uncomfortably long catheter investigation. As a study limitation, the short observation interval may have caused carryover effects of the first to the second period as suggested by FIG. 5. However, this still allowed for the interpretation of the study, that both drugs are potent pulmonary vasodilators and that treprostinil effects are significantly sustained compared to the iloprost effects.

The longer duration of action and the virtual absence of side effects (except the bitter taste of treprostinil aerosol, later attributed to metacresol) encouraged increasing the applied treprostinil dose in study ii). Observation time was

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extended to 3 hours to obtain precise pharmacodynamic data. Inhaled treprostinil resulted in a strong pulmonary vasodilation that outlasted the observation time of 3 hours when compared to placebo inhalation. Surprisingly, inhaled treprostinil was tolerated in doses up to 90 µg.

Study iii) successfully demonstrated that the inhalation time could be reduced to literally one single breath of 2000 µg/ml treprostinil solution, thereby applying a dose of 15 µg. This drug administration with a single breath induced pulmonary vasodilation for longer than 3 hours compared to placebo inhalation. Side effects were minor, of low frequency and not related to drug concentration. It was a surprising finding that such high concentrations of treprostinil were so well tolerated.

Conclusion:

Inhaled treprostinil can be applied in high doses (up to 90 µg) with a minimal inhalation time. Inhaled treprostinil exerts high pulmonary selectivity and leads to a long-lasting pulmonary vasodilation.

Although the foregoing refers to particular preferred embodiments, it will be understood that the present invention is not so limited. It will occur to those of ordinary skill in the art that various modifications may be made to the disclosed embodiments and that such modifications are intended to be within the scope of the present invention.

All of the publications, patent applications and patents cited in this specification are incorporated herein by reference in their entirety.

What is claimed is:

1. A method of treating pulmonary hypertension comprising: administering by inhalation to a human suffering from pulmonary hypertension a therapeutically effective single event dose of a formulation comprising from 200 to 1000 µg/ml of treprostinil or a pharmaceutically acceptable salt thereof with a pulsed ultrasonic nebulizer that aerosolizes a fixed amount of treprostinil or a pharmaceutically acceptable salt thereof per pulse, said pulsed ultrasonic nebulizer comprising an opto-acoustical trigger that allows said human to synchronize each breath to each pulse, said therapeutically effective single event dose comprising from 15 µg to 90 µg of treprostinil or a pharmaceutically acceptable salt thereof delivered in 3 to 18 breaths, wherein the fixed amount of treprostinil or its pharmaceutically acceptable salt for each breath inhaled by the human comprises at least 5 µg of treprostinil or its pharmaceutically acceptable salt.

2. The method of claim 1, wherein the single event dose produces a peak plasma concentration of treprostinil below 1.74 ng/ml about 10-15 minutes after the single event dose.

3. The method of claim 1, wherein the formulation comprises 600 µg/ml of the treprostinil or its pharmaceutically acceptable salt thereof.

4. The method of claim 1, wherein the single event dose is not repeated for a period of at least 3 hours.

* * * * *

EXHIBIT 16



US010716793B2

(12) **United States Patent**
Olschewski et al.(10) **Patent No.: US 10,716,793 B2**(45) **Date of Patent: *Jul. 21, 2020**(54) **TREPROSTINIL ADMINISTRATION BY INHALATION**(71) Applicant: **United Therapeutics Corporation**,
Silver Spring, MD (US)(72) Inventors: **Horst Olschewski**, Graz (AT); **Robert Roscigno**, Chapel Hill, NC (US); **Lewis J. Rubin**, LaJolla, CA (US); **Thomas Schmehl**, Giessen (DE); **Werner Seeger**, Giessen (DE); **Carl Sterritt**, Weybridge (GB); **Robert Voswinckel**, Giessen (DE)(73) Assignee: **United Therapeutics Corporation**,
Silver Spring, MD (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **16/778,662**(22) Filed: **Jan. 31, 2020**(65) **Prior Publication Data**

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Related U.S. Application Data

(60) Continuation of application No. 16/536,954, filed on Aug. 9, 2019, which is a continuation of application No. 15/011,999, filed on Feb. 1, 2016, now Pat. No. 10,376,525, which is a division of application No. 13/469,854, filed on May 11, 2012, now Pat. No. 9,339,507, which is a division of application No. 12/591,200, filed on Nov. 12, 2009, now Pat. No. 9,358,240, which is a continuation of application No. 11/748,205, filed on May 14, 2007, now abandoned.

(60) Provisional application No. 60/800,016, filed on May 15, 2006.

(51) **Int. Cl.****A61K 31/557** (2006.01)**A61K 9/00** (2006.01)**A61K 31/192** (2006.01)(52) **U.S. Cl.**CPC **A61K 31/557** (2013.01); **A61K 9/008** (2013.01); **A61K 9/0078** (2013.01); **A61K 31/192** (2013.01)(58) **Field of Classification Search**

None

See application file for complete search history.

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Primary Examiner — Jeffrey S Lundgren*Assistant Examiner* — Michael J Schmitt(74) *Attorney, Agent, or Firm* — Foley & Lardner LLP(57) **ABSTRACT**

Treprostinil can be administered using a metered dose inhaler. Such administration provides a greater degree of autonomy to patients. Also disclosed are kits that include a metered dose inhaler containing a pharmaceutical formulation containing treprostinil.

8 Claims, 12 Drawing Sheets**UTC_PH-ILD_009772**

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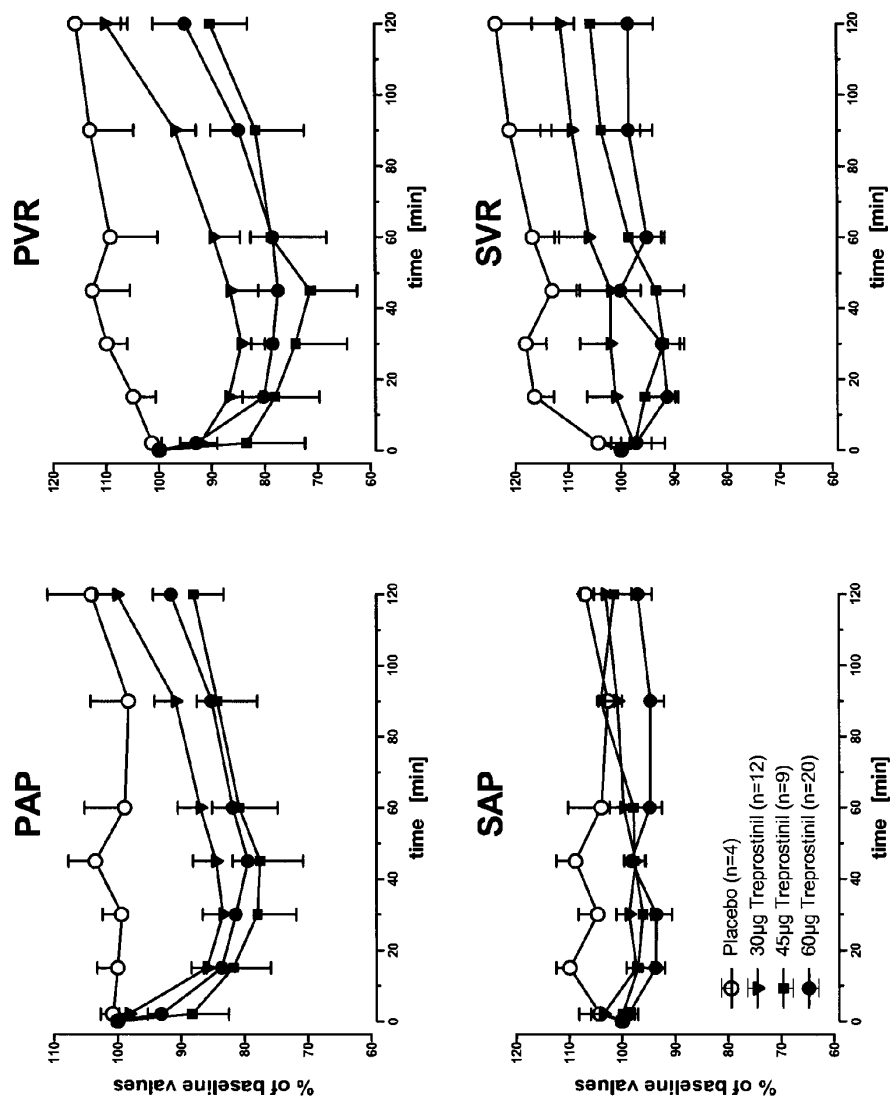
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FIGURE 1



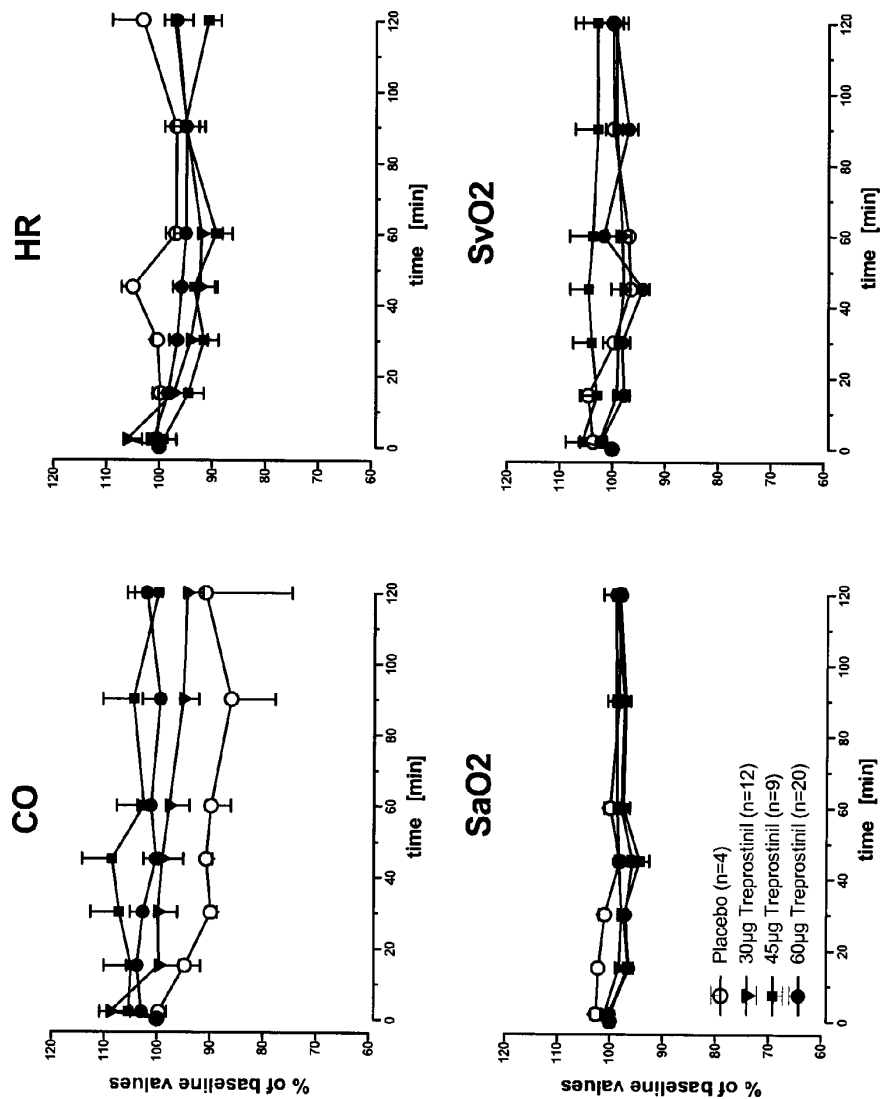
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FIGURE 2



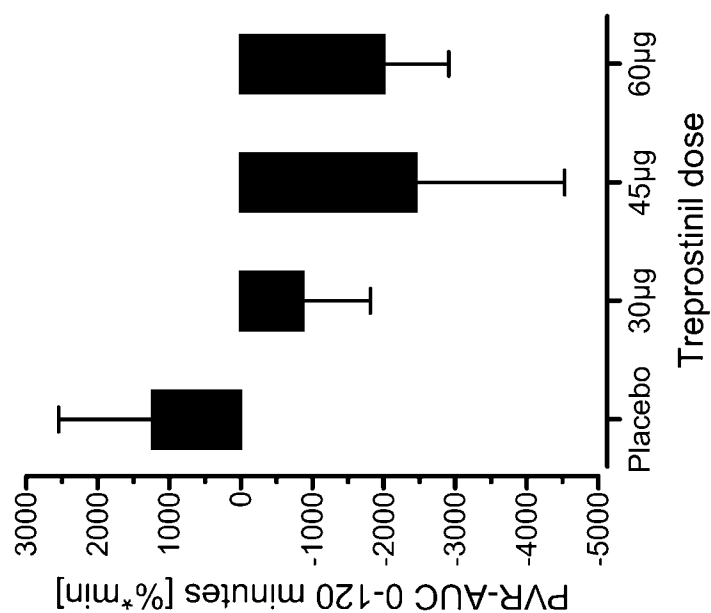
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FIGURE 3



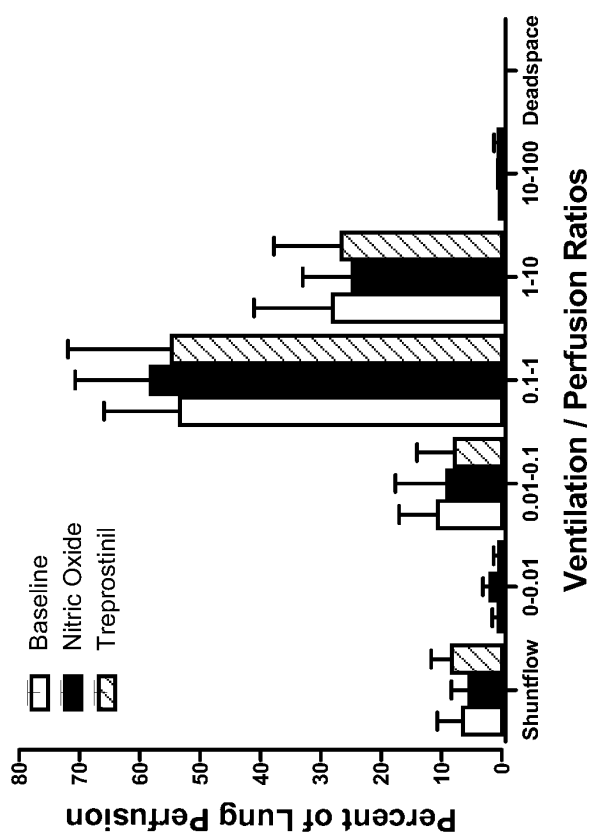
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FIGURE 4



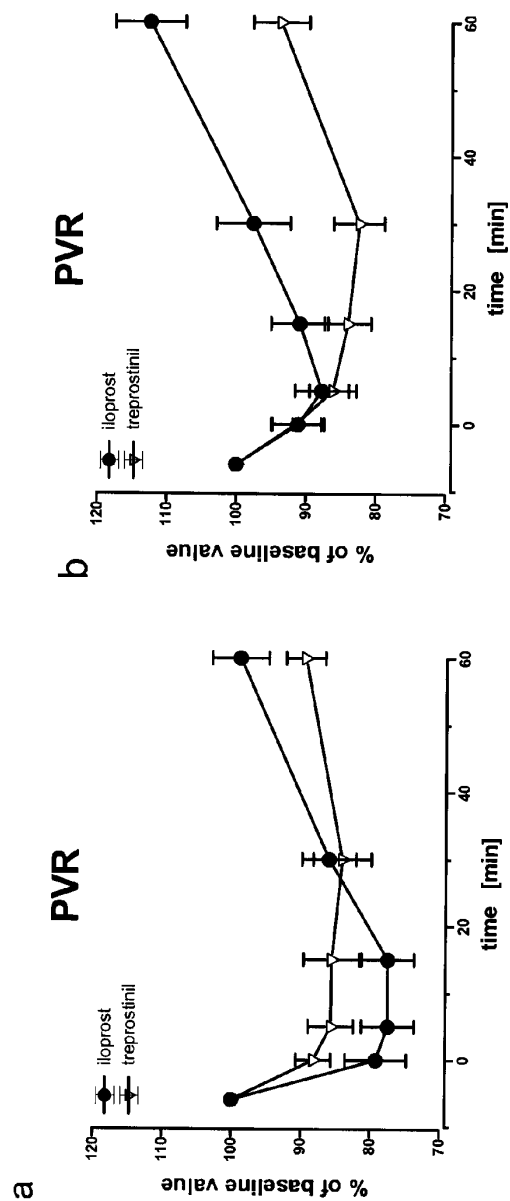
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FIGURE 5



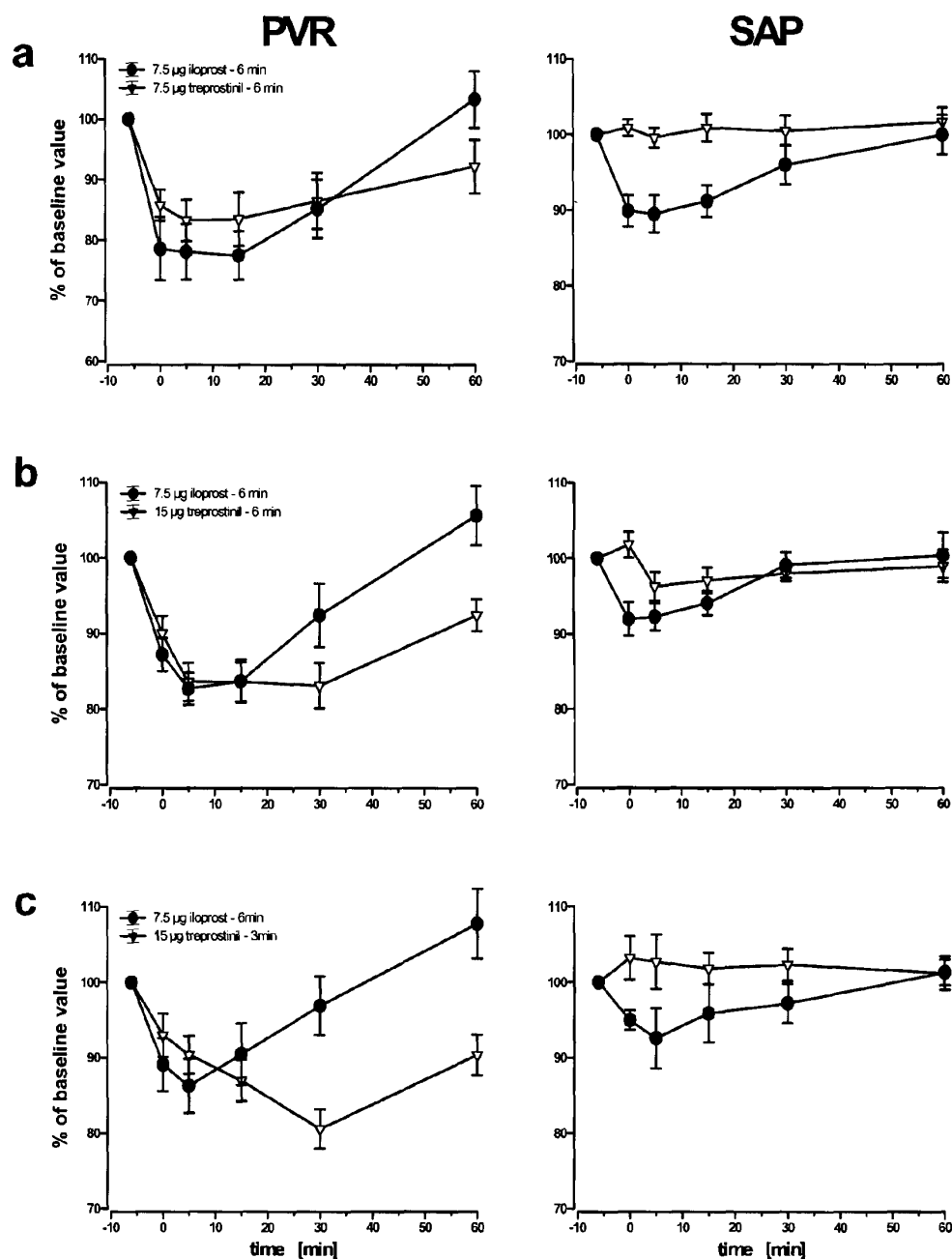
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FIGURE 6



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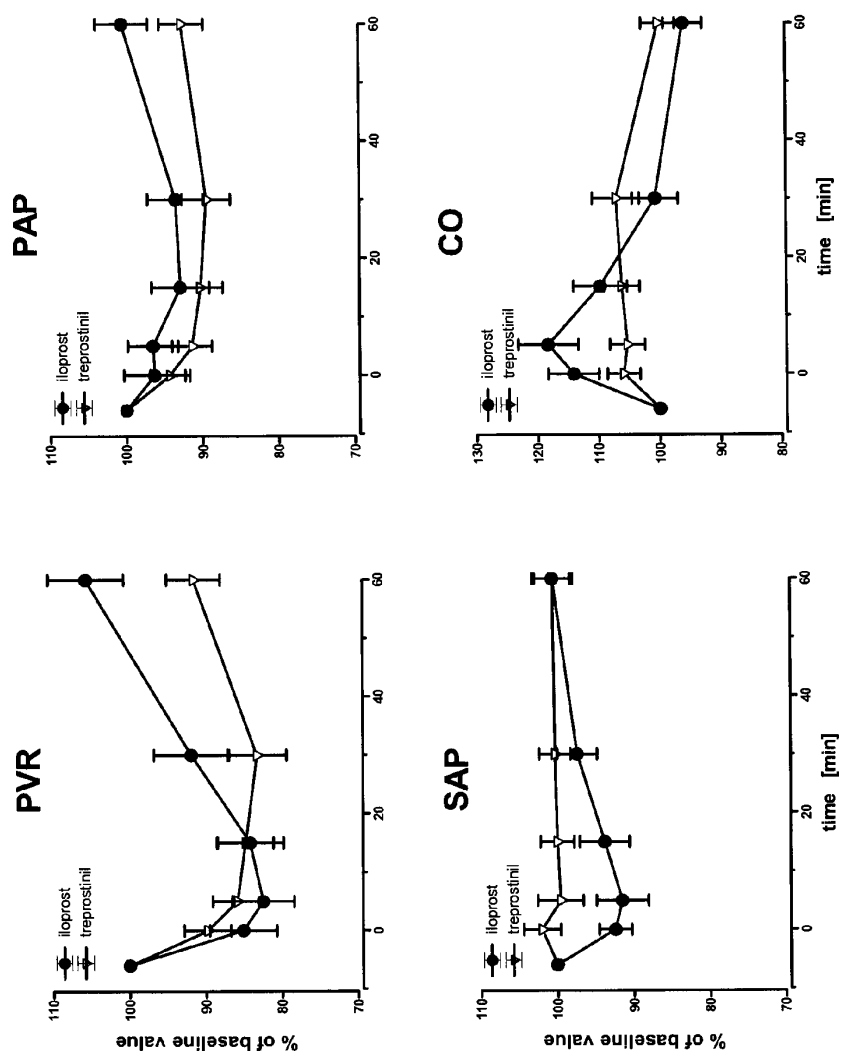
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FIGURE 7



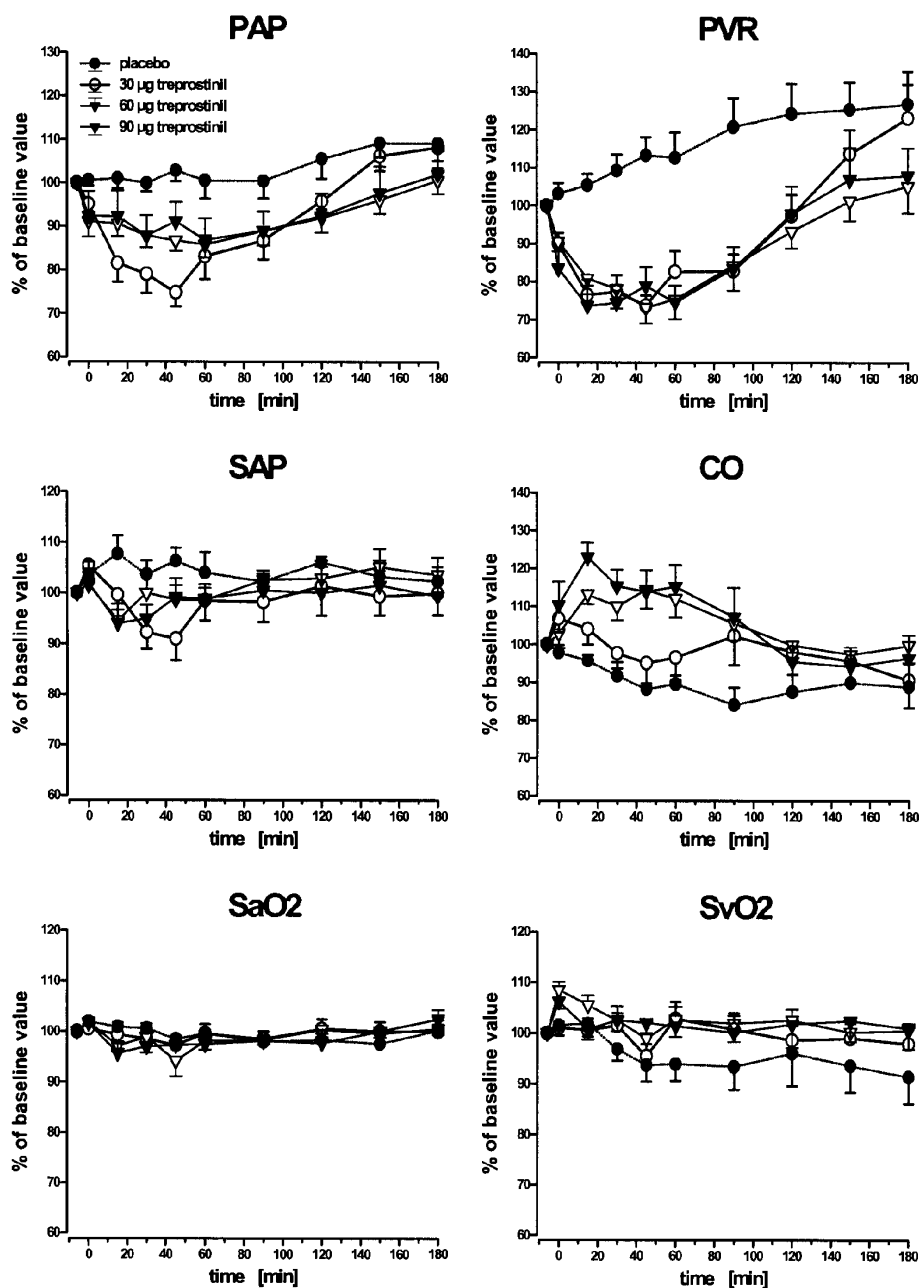
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FIGURE 8



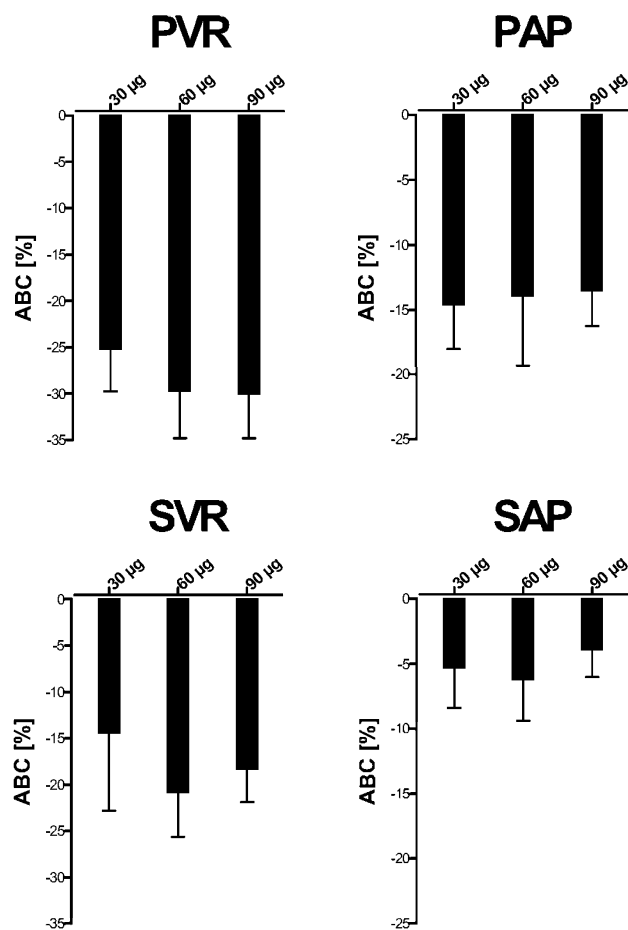
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FIGURE 9



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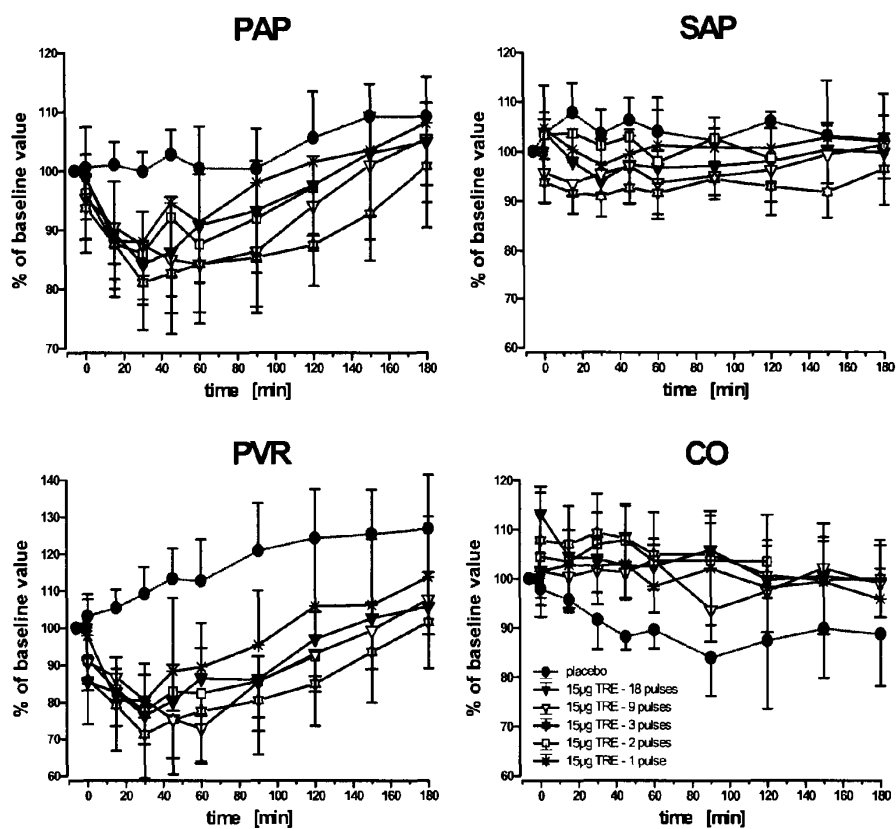
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FIGURE 10



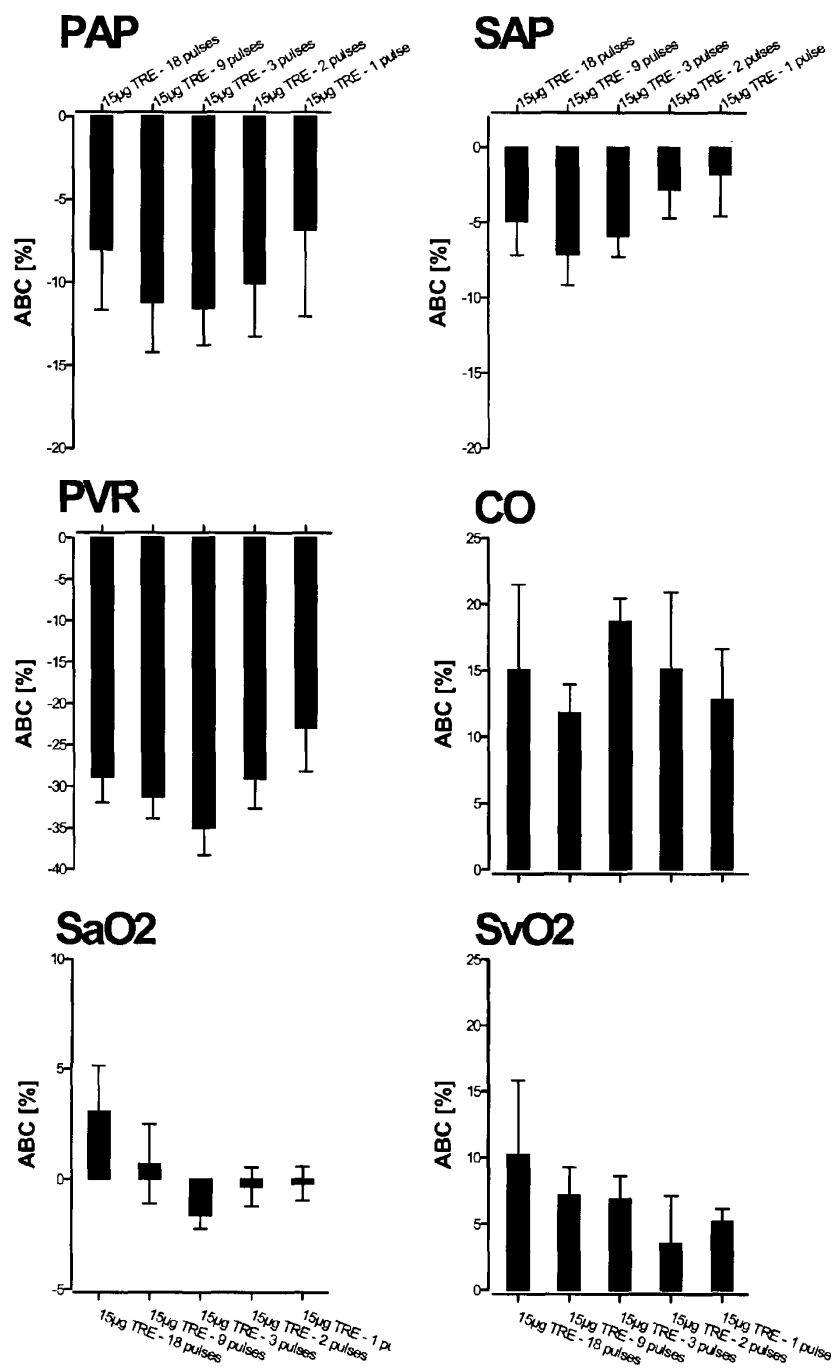
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FIGURE 11



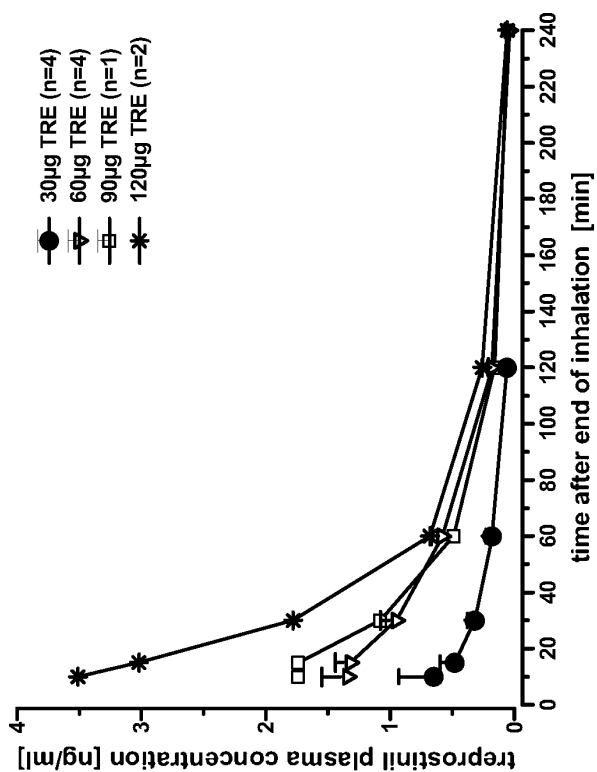
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FIGURE 12



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1 **TREPROSTINIL ADMINISTRATION BY INHALATION**

CROSS REFERENCE TO RELATED APPLICATIONS

The present application is a Continuation of U.S. application Ser. No. 16/536,954, filed Aug. 9, 2019, which is a Continuation of U.S. application Ser. No. 15/011,999, filed Feb. 1, 2016, which is a Divisional of U.S. application Ser. No. 13/469,854, filed May 11, 2012, Divisional of U.S. application Ser. No. 12/591,200, filed Nov. 12, 2009, which is a Continuation of U.S. application Ser. No. 11/748,205, filed May 14, 2007, which claims priority to U.S. provisional application No. 60/800,016 filed May 15, 2006, which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

The present application relates to methods and kits for therapeutic treatment and, more particularly, to therapeutic methods involving administering treprostinil using a metered dose inhaler and related kits.

BACKGROUND OF THE INVENTION

All blood is driven through the lungs via the pulmonary circulation in order, among other things, to replenish the oxygen which it dispenses in its passage around the rest of the body via the systemic circulation. The flow through both circulations is in normal circumstances equal, but the resistance offered to it in the pulmonary circulation is generally much less than that of the systemic circulation. When the resistance to pulmonary blood flow increases, the pressure in the circulation is greater for any particular flow. The above described condition is referred to as pulmonary hypertension (PH). Generally, pulmonary hypertension is defined through observations of pressures above the normal range pertaining in the majority of people residing at the same altitude and engaged in similar activities.

Pulmonary hypertension may occur due to various reasons and the different entities of pulmonary hypertension were classified based on clinical and pathological grounds in 5 categories according to the latest WHO convention, see e.g. Simonneau G., et al. J. Am. Coll. Cardiol. 2004; 43(12 Suppl S):S5-S12S. Pulmonary hypertension can be a manifestation of an obvious or explicable increase in resistance, such as obstruction to blood flow by pulmonary emboli, malfunction of the heart's valves or muscle in handling blood after its passage through the lungs, diminution in pulmonary vessel caliber as a reflex response to alveolar hypoxia due to lung diseases or high altitude, or a mismatch of vascular capacity and essential blood flow, such as shunting of blood in congenital abnormalities or surgical removal of lung tissue. In addition, certain infectious diseases, such as HIV and liver diseases with portal hypertension may cause pulmonary hypertension. Autoimmune disorders, such as collagen vascular diseases, also often lead to pulmonary vascular narrowing and contribute to a significant number of pulmonary hypertension patients. The cases of pulmonary hypertension remain where the cause of the increased resistance is as yet inexplicable are defined as idiopathic (primary) pulmonary hypertension (iPAH) and are diagnosed by and after exclusion of the causes of secondary pulmonary hypertension and are in the majority of cases related to a genetic mutation in the bone morphogenetic protein receptor-2 gene. The cases of idiopathic

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pulmonary arterial hypertension tend to comprise a recognizable entity of about 40% of patients cared for in large specialized pulmonary hypertension centers. Approximately 65% of the most commonly afflicted are female and young adults, though it has occurred in children and patients over 50. Life expectancy from the time of diagnosis is short without specific treatment, about 3 to 5 years, though occasional reports of spontaneous remission and longer survival are to be expected given the nature of the diagnostic process. Generally, however, disease progress is inexorable via syncope and right heart failure and death is quite often sudden.

Pulmonary hypertension refers to a condition associated with an elevation of pulmonary arterial pressure (PAP) over normal levels. In humans, a typical mean PAP is approximately 12-15 mm Hg. Pulmonary hypertension, on the other hand, can be defined as mean PAP above 25 mmHg, assessed by right heart catheter measurement. Pulmonary arterial pressure may reach systemic pressure levels or even exceed these in severe forms of pulmonary hypertension. When the PAP markedly increases due to pulmonary venous congestion, i.e. in left heart failure or valve dysfunction, plasma can escape from the capillaries into the lung interstitium and alveoli. Fluid buildup in the lung (pulmonary edema) can result, with an associated decrease in lung function that can in some cases be fatal. Pulmonary edema, however, is not a feature of even severe pulmonary hypertension due to pulmonary vascular changes in all other entities of this disease.

Pulmonary hypertension may either be acute or chronic. Acute pulmonary hypertension is often a potentially reversible phenomenon generally attributable to constriction of the smooth muscle of the pulmonary blood vessels, which may be triggered by such conditions as hypoxia (as in high-altitude sickness), acidosis, inflammation, or pulmonary embolism. Chronic pulmonary hypertension is characterized by major structural changes in the pulmonary vasculature, which result in a decreased cross-sectional area of the pulmonary blood vessels. This may be caused by, for example, chronic hypoxia, thromboembolism, collagen vascular diseases, pulmonary hypercirculation due to left-to-right shunt, HIV infection, portal hypertension or a combination of genetic mutation and unknown causes as in idiopathic pulmonary arterial hypertension.

Pulmonary hypertension has been implicated in several life-threatening clinical conditions, such as adult respiratory distress syndrome ("ARDS") and persistent pulmonary hypertension of the newborn ("PPHN"). Zapol et al., Acute Respiratory Failure, p. 241-273, Marcel Dekker, New York (1985); Peckham, J. Ped. 93:1005 (1978). PPHN, a disorder that primarily affects full-term infants, is characterized by elevated pulmonary vascular resistance, pulmonary arterial hypertension, and right-to-left shunting of blood through the patent ductus arteriosus and foramen ovale of the newborn's heart. Mortality rates range from 12-50%. Fox, Pediatrics 59:205 (1977); Dworetz, Pediatrics 84:1 (1989). Pulmonary hypertension may also ultimately result in a potentially fatal heart condition known as "cor pulmonale," or pulmonary heart disease. Fishman, "Pulmonary Diseases and Disorders" 2nd Ed., McGraw-Hill, New York (1988).

Currently, there is no treatment for pulmonary hypertension that can be administered using a compact inhalation device, such as a metered dose inhaler.

SUMMARY OF THE INVENTION

One embodiment is a method of delivering to a subject in need thereof a therapeutically effective amount of trepros-

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tinil, or treprostinil derivative or a pharmaceutically acceptable salt thereof comprising administering to the subject a therapeutically effective amount of the treprostinil or treprostinil derivative or a pharmaceutically acceptable salt thereof using a metered dose inhaler.

Another embodiment is a method for treating pulmonary hypertension comprising administering to a subject in need thereof treprostinil or its derivative, or a pharmaceutically acceptable salt thereof using a metered dose inhaler.

Yet another embodiment is a kit comprising a metered dose inhaler containing a pharmaceutical formulation comprising treprostinil or treprostinil derivative, or a pharmaceutically acceptable salt thereof.

And yet another embodiment is a kit for treating pulmonary hypertension in a subject, comprising (i) an effective amount of treprostinil or its derivative, or a pharmaceutically acceptable salt thereof; (ii) a metered dose inhaler; (iii) instructions for use in treating pulmonary hypertension.

Administration of treprostinil using a metered dose inhaler can provide patients, such as pulmonary hypertension patients, with a high degree of autonomy.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 pulmonary and systemic changes in hemodynamics following the inhalation of placebo (open circles), 30 μ g treprostinil (triangles), 45 μ g treprostinil (squares) or 60 μ g TREprostinil (black circles) applied by a Metered Dose Inhaler (MDI-TRE). A single short inhalation of treprostinil induced sustained reduction of PAP and PVR that outlasted the observation period of 120 minutes at doses of 45 and 60 μ g MDI-TRE. Systemic arterial pressure and resistance were not significantly affected. PAP=mean pulmonary artery pressure; PVR=pulmonary vascular resistance; SAP=mean systemic arterial pressure; SVR=systemic vascular resistance. Data are given as mean value \pm standard error of the mean (SEM).

FIG. 2 presents hemodynamic changes induced by the inhalation of placebo (open circles), 30 μ g treprostinil (triangles), 45 μ g treprostinil (squares) or 60 μ g treprostinil (black circles) applied by a metered dose inhaler. Treprostinil induced sustained elevation of cardiac output. Heart rate was rather unchanged as a sign for low spillover of MDI-TRE to the systemic circulation. Gas exchange was not negatively affected. CO=cardiac output; HR=heart rate; SaO₂=arterial oxygen saturation; SvO₂=central venous oxygen saturation. Data are given as mean value \pm SEM.

FIG. 3 shows areas under the curve for changes in pulmonary vascular resistance (PVR) calculated for an observation period of 120 minutes after inhalation treprostinil using a metered dose inhaler. PVR was markedly lowered by treprostinil inhalation. The increased pulmonary vasodilation over time with the two highest doses mainly relies on the more sustained effect over time. Data are shown as mean value \pm 95% confidence intervals.

FIG. 4 demonstrates Ventilation-perfusion matching measured with the multiple inert gas elimination technique. Five patients (30 μ g TRE, n=2; 45 μ g TRE, n=1; 60 μ g TRE, n=2) with pre-existing gas exchange problems were investigated for changes in ventilation-perfusion ratios. All patients had significant shunt flow at baseline. Shunt-flow and low V/Q areas were not significantly changed by nitric oxide (NO) inhalation or treprostinil inhalation using a metered dose inhaler (MDI-TRE). MDI-TRE applied at high treprostinil concentrations did not negatively affect ventilation-perfusion matching and gas-exchange. Data are given as mean value \pm 95% confidence intervals.

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FIG. 5 presents response of pulmonary vascular resistance (PVR) to inhaled treprostinil vs. iloprost—period effects. a) First inhalation with treprostinil (n=22) vs. first inhalation with iloprost (n=22); b) second inhalation with treprostinil (n=22) vs. second inhalation with iloprost (n=22). The PVR decrease with treprostinil was delayed and prolonged, compared to iloprost. Due to carryover effects from the first period, in the second period, the effects of both drugs appeared shortened. Data are shown as percent of baseline values (mean value \pm 95% confidence interval).

FIG. 6 presents response of PVR and systemic arterial pressure (SAP) to inhalation of treprostinil vs. iloprost—dose effects. a) Inhalation of 7.5 μ g iloprost (in 6 min) vs. 7.5 μ g treprostinil (6 min) (n=14, in a randomized order). b) Inhalation of 7.5 μ g iloprost (6 min) vs. 15 μ g treprostinil (6 min) (n=14, in randomized order). c) Inhalation of 7.5 μ g iloprost (6 min) vs. 15 μ g treprostinil (3 min) (n=16, in randomized order). Data are shown as percent of baseline values (mean \pm 95% confidence interval). Iloprost, filled circles; Treprostinil, open triangles.

FIG. 7 presents hemodynamic response to inhalation of treprostinil vs. iloprost. Data from n=44 patients, who inhaled both drugs in randomized order, shown as percent of baseline values (mean value \pm 95% confidence interval). PVR, pulmonary vascular resistance; PAP, mean pulmonary arterial pressure; SAP, mean systemic arterial pressure; CO, cardiac output.

FIG. 8 presents pharmacodynamics after treprostinil inhalation vs. placebo. Placebo or treprostinil in doses of 30 μ g, 60 μ g or 90 μ g were inhaled (means \pm 95% confidence intervals). Maximal decrease of PVR was comparable for all doses. The duration of pulmonary vasodilation (PVR-decrease) appeared to be dose dependent. PVR, pulmonary vascular resistance; PAP, mean pulmonary arterial pressure; SAP, mean systemic arterial pressure; CO, cardiac output; SaO₂, arterial oxygen saturation; SvO₂, mixed venous oxygen saturation.

FIG. 9 presents Areas Between the placebo and the treprostinil Curves (ABC). ABCs were calculated for a 3-hour period after inhalation of TRE or placebo from the relative changes of hemodynamic parameters (means \pm 95% confidence intervals). PVR, pulmonary vascular resistance; PAP, mean pulmonary arterial pressure; SAP, mean systemic arterial pressure; SVR, systemic vascular resistance.

FIG. 10 presents hemodynamic responses to the inhalation of 15 μ g treprostinil. The inhalation time by increasing treprostinil concentration. A pulse of aerosol was generated every 6 seconds. TRE aerosol was inhaled in concentrations of 100 μ g/ml (18 pulses; n=6), 200 μ g/ml (9 pulses; n=6), 600 μ g/ml (3 pulses; n=21), 1000 μ g/ml (2 pulses; n=7) and 2000 μ g/ml (1 pulse; n=8). Placebo data correspond to FIG. 8. Data are shown as means \pm 95% confidence intervals. PVR, pulmonary vascular resistance; PAP, mean pulmonary arterial pressure; SAP, mean systemic arterial pressure; CO, cardiac output.

FIG. 11 presents areas between the placebo curve and the responses to 15 μ g treprostinil applied at increasing concentrations to minimize inhalation time. Mean \pm SEM of relative changes of hemodynamic parameters (observation time 120 min). PAP, pulmonary arterial pressure, SAP, systemic arterial pressure, PVR, pulmonary vascular resistance, CO, cardiac output, SaO₂, systemic arterial oxygen saturation, SvO₂, pulmonary arterial oxygen saturation.

FIG. 12 presents pharmacokinetics of treprostinil after a single inhalation. Treprostinil plasma levels after inhalation of 30 μ g, 60 μ g, 90 μ g or 120 μ g treprostinil (6 min

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inhalation period; experiments correspond to those shown in FIGS. 8 and 9). Data with error bars represent mean values \pm SEM.

DETAILED DESCRIPTION OF THE INVENTION

Unless otherwise specified, the term “a” or “an” used herein shall mean “one or more.”

The present application incorporates herein by reference in its entirety Voswinckel R, et al. J. Am. Coll. Cardiol. 2006; 48:1672-1681.

The inventors discovered that a therapeutically effective dose of treprostinil can be administered in a few single inhalations using a compact inhalation device, such as a metered dose inhaler. Furthermore, the inventors discovered that such administering does not cause significant side effects, especially no significant side effects related to systemic blood pressure and circulation as well as no gas exchange deteriorations or disruptions.

Accordingly, one embodiment of the invention is a method of delivering to a subject in need thereof, such as a human being, a therapeutically effective amount of treprostinil comprising administering to the subject a formulation comprising a therapeutically effective amount of treprostinil, its derivative or a pharmaceutically acceptable salt thereof using a metered dose inhaler. Treprostinil can be administered via a metered dose inhaler to a subject affected with a condition or disease, which can be treated by treprostinil, such as asthma, pulmonary hypertension, peripheral vascular disease or pulmonary fibrosis.

Another embodiment of the invention is a method for treating pulmonary hypertension, comprising administering to a subject in need thereof, such as a human being, treprostinil or its derivative, or a pharmaceutically acceptable salt using a metered dose inhaler.

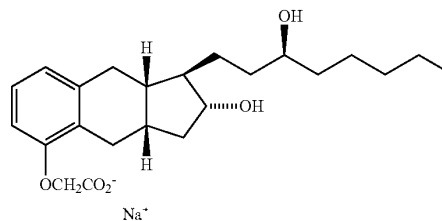
Treprostinil, or 9-deoxy-2',9- α -methano-3-oxa-4,5,6-trinor-3,7-(1'3'-interphenylene)-13,14-dihydro-prostaglandin F₁, is a prostacyclin analogue, first described in U.S. Pat. No. 4,306,075. U.S. Pat. No. 5,153,222 describes use of treprostinil for treatment of pulmonary hypertension. Treprostinil is approved for the intravenous as well as subcutaneous route, the latter avoiding septic events associated with continuous intravenous catheters. U.S. Pat. Nos. 6,521,212 and 6,756,033 describe administration of treprostinil by inhalation for treatment of pulmonary hypertension, peripheral vascular disease and other diseases and conditions. U.S. Pat. No. 6,803,386 discloses administration of treprostinil for treating cancer such as lung, liver, brain, pancreatic, kidney, prostate, breast, colon and head-neck cancer. US patent application publication No. 2005/0165111 discloses treprostinil treatment of ischemic lesions. U.S. Pat. No. 7,199,157 discloses that treprostinil treatment improves kidney functions. US patent application publication No. 2005/0282903 discloses treprostinil treatment of neuropathic foot ulcers. U.S. provisional application No. 60/900,320 filed Feb. 9, 2007, discloses treprostinil treatment of pulmonary fibrosis.

The term “acid derivative” is used herein to describe C1-4 alkyl esters and amides, including amides wherein the nitrogen is optionally substituted by one or two C1-4 alkyl groups.

The present invention also encompasses methods of using Treprostinil or its derivatives, or pharmaceutically acceptable salts thereof. In one embodiment, a method uses Treprostinil sodium, currently marketed under the trade name of REMODULIN®. The FDA has approved Trepro-

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stinil sodium for the treatment of pulmonary arterial hypertension by injection of dose concentrations of 1.0 mg/mL, 2.5 mg/mL, 5.0 mg/mL and 10.0 mg/mL. The chemical structure formula for Treprostinil sodium is:



Treprostinil sodium is sometimes designated by the chemical names: (a) [(1R,2R,3aS,9aS)-2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[*f*]inden-5-yl]oxy]acetic acid; or (b) 9-deoxy-2',9- α -methano-3-oxa-4,5,6-trinor-3,7-(1'3'-interphenylene)-13,14-dihydro-prostaglandin F₁. Treprostinil sodium is also known as: UT-15; LRX-15; 15AU81; UNIPROST™; BW A15AU; and U-62,840. The molecular weight of Treprostinil sodium is 390.52, and its empirical formula is C₂₃H₃₄O₅.

In certain embodiments, treprostinil can be administered in combination with one or more additional active agents. In some embodiments, such one or more additional active agents can be also administered together with treprostinil using a metered dose inhaler. Yet in some embodiments, such one or more additional active agents can be administered separately from treprostinil. Particular additional active agents that can be administered in combination with treprostinil may depend on a particular disease or condition for treatment or prevention of which treprostinil is administered. In some cases, the additional active agent can be a cardiovascular agent such as a calcium channel blocker, a phosphodiesterase inhibitor, an endothelial antagonist, or an antiplatelet agent.

The present invention extends to methods of using physiologically acceptable salts of Treprostinil, as well as non-physiologically acceptable salts of Treprostinil that may be used in the preparation of the pharmacologically active compounds of the invention.

The term “pharmaceutically acceptable salt” refers to a salt of Treprostinil with an inorganic base, organic base, inorganic acid, organic acid, or basic or acidic amino acid. Salts of inorganic bases can be, for example, salts of alkali metals such as sodium or potassium; alkaline earth metals such as calcium and magnesium or aluminum; and ammonia. Salts of organic bases can be, for example, salts trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, and triethanolamine. Salts of inorganic acids can be, for example, salts of hydrochloric acid, hydroboric acid, nitric acid, sulfuric acid, and phosphoric acid. Salts of organic acids can be, for example, salts of formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, lactic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, and p-toluenesulfonic acid. Salts of basic amino acids can be, for example, salts of arginine, lysine and ornithine. Salts of acidic amino acids can include, for example, salts of aspartic acid and glutamic acid. Quaternary ammonium salts can be formed, for example, by reaction with lower alkyl halides, such as methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides, with dialkyl sul-

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phates, with long chain halides, such as decyl, lauryl, myristyl, and stearyl chlorides, bromides, and iodides, and with aralkyl halides, such as benzyl and phenethyl bromides.

Preferred pharmaceutically acceptable salts are disclosed, for example, in US patent application publication No. 20050085540.

Treprostinil can be administered by inhalation, which in the present context refers to the delivery of the active ingredient or a combination of active ingredients through a respiratory passage, wherein the subject in need of the active ingredient(s) through the subject's airways, such as the subject's nose or mouth.

A metered dose inhaler in the present context means a device capable of delivering a metered or bolus dose of respiratory drug, such as treprostinil, to the lungs. One example of the inhalation device can be a pressurized metered dose inhaler, a device which produces the aerosol clouds for inhalation from solutions and/or suspensions of respiratory drugs in chlorofluorocarbon (CFC) and/or hydrofluoroalkane (HFA) solutions.

The inhalation device can be also a dry powder inhaler. In such case, the respiratory drug is inhaled in solid formulation, usually in the form of a powder with particle size less than 10 micrometers in diameter or less than 5 micrometers in diameter.

The metered dose inhaler can be a soft mist inhaler (SMI), in which the aerosol cloud containing a respiratory drug can be generated by passing a solution containing the respiratory drug through a nozzle or series of nozzles. The aerosol generation can be achieved in SMI, for example, by mechanical, electromechanical or thermomechanical process. Examples of soft mist inhalers include the Respimat® Inhaler (Boeinger Ingelheim GmbH), the AERx® Inhaler (Aradigm Corp.), the Mystic™ Inhaler (Ventaira Pharmaceuticals, Inc) and the Aira™ Inhaler (Chrysalis Technologies Incorporated). For a review of soft mist inhaler technology, see e.g. M. Hindle, The Drug Delivery Companies Report, Autumn/Winter 2004, pp. 31-34. The aerosol for SMI can be generated from a solution of the respiratory drug further containing pharmaceutically acceptable excipients. In the present case, the respiratory drug is treprostinil, its derivative or a pharmaceutically acceptable salt thereof, which can be formulated in SMI is as a solution. The solution can be, for example, a solution of treprostinil in water, ethanol or a mixture thereof. Preferably, the diameter of the treprostinil-containing aerosol particles is less than about 10 microns, or less than about 5 microns, or less than about 4 microns.

Treprostinil concentration in an aerosolable formulation, such as a solution, used in a metered dose inhaler can range from about 500 µg/ml to about 2500 µg/ml, or from about 800 µg/ml to about 2200 µg/ml, or from about 1000 µg/ml to about 2000 µg/ml.

The dose of treprostinil that can be administered using a metered dose inhaler in a single event can be from about 15 µg to about 100 µg or from about 15 µg to about 90 µg or from about 30 µg to about 90 µg or from about 30 µg to about 60 µg.

Administering of treprostinil in a single event can be carried out in a limited number of breaths by a patient. For example, treprostinil can be administered in 20 breaths or less, or in 10 breaths or less, or than 5 breaths or less. Preferably, treprostinil is administered in 3, 2 or 1 breaths.

The total time of a single administering event can be less than 5 minutes, or less than 1 minute, or less than 30 seconds.

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Treprostinil can be administered a single time per day or several times per day.

In some embodiments, the method of treatment of pulmonary hypertension can further comprise administering at least one supplementary agent selected from the group consisting of sildenafil, tadalafil, calcium channel blockers (diltiazem, amlodipine, nifedipine), bosentan, sitaxsentan, ambrisentan, and pharmaceutically acceptable salts thereof. In some embodiments, the supplementary agents can be included in the treprostinil formulation and, thus, can be administered simultaneously with treprostinil using a metered dose inhaler. In some embodiments, the supplementary agents can be administered separately from treprostinil. In some embodiments, the application of intravenous prostacyclin (flolan), intravenous iloprost or intravenous or subcutaneous treprostinil can be administered in addition to treprostinil administered via inhalation using a metered dose inhaler.

The present invention also provides a kit that includes a metered dose inhaler containing a pharmaceutical formulation comprising treprostinil or its derivative, or a pharmaceutically acceptable salt thereof. Such a kit can further include instructions on how to use the metered dose inhaler for inhaling treprostinil. Such instructions can include, for example, information on how to coordinate patient's breathing, and actuation of the inhaler. The kit can be used by a subject, such as human being, affected with a disease or condition that can be treated by treprostinil, such as asthma, pulmonary hypertension, peripheral vascular disease or pulmonary fibrosis.

In some cases, the kit is a kit for treating pulmonary hypertension, that includes (i) a metered dose inhaler containing a pharmaceutical formulation comprising treprostinil or its derivative, or a pharmaceutically acceptable salt thereof; and (ii) instructions for use of the metered dose inhaler containing treprostinil in treating pulmonary hypertension.

As used herein, the phrase "instructions for use" shall mean any FDA-mandated labeling, instructions, or package inserts that relate to the administration of Treprostinil or its derivatives, or pharmaceutically acceptable salts thereof, for treatment of pulmonary hypertension by inhalation. For example, instructions for use may include, but are not limited to, indications for pulmonary hypertension, identification of specific symptoms associated with pulmonary hypertension, that can be ameliorated by Treprostinil, recommended dosage amounts for subjects suffering from pulmonary hypertension and instructions on coordination of individual's breathing and actuation of the metered dose inhaler.

The present invention can be illustrated in more detail by the following example, however, it should be understood that the present invention is not limited thereto.

Example 1

Open Label Study Upon Acute Safety, Tolerability and Hemodynamic Effects of Inhaled Treprostinil Delivered in Seconds

A study was conducted of acute vasodilator challenge during right heart catheter investigation to determine the safety, tolerability and pulmonary vasodilatory potency of inhaled treprostinil applied in seconds by a soft mist inhaler (SMI-TRE). The study produced evidence for a long lasting

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favourable effect of SMI-TRE on pulmonary hemodynamics in absence of systemic side effects and gas exchange disruptions.

Summary:

Inhaled nitric oxide (20 ppm; n=45) and inhaled treprostinil sodium (TRE; n=41) or placebo (n=4) were applied once during right heart catheter investigation. TRE was delivered in 2 breaths (1000 µg/ml aerosol concentration; 30 µg dose; n=12), 3 breaths (1000 µg/ml; 45 µg; n=9) or 2 breaths (2000 µg/ml; 60 µg; n=20) from a Respimat® SMI. Pulmonary hemodynamics and blood gases were measured at defined time points, observation time following TRE application was 120 minutes. TRE doses of 30 µg, 45 µg and 60 µg reduced pulmonary vascular resistance (PVR) to 84.4±8.7%, 71.4±17.5% and 77.5±7.2% of baseline values, respectively (mean±95% confidence interval). The 120 minute area under the curve for PVR for placebo, 30 µg, 45 µg and 60 µg TRE was 1230±1310, -870±940, -2450±2070 and -2000±900 min %, respectively. Reduction of PVR by a single inhalation of the two higher doses outlasted the observation period of 120 minutes. Reduction of systemic vascular resistance and pressure was negligible, showing a high pulmonary selectivity for SMI-TRE. Intrapulmonary selectivity was also provided by SMI-TRE as ventilation/perfusion matching, assessed by the multiple inert gas elimination technique in 5 patients with gas exchange problems, was not significantly different after SMI-TRE compared to inhaled nitric oxide or no treatment. No significant side effects were observed.

Conclusions: The acute application of inhaled treprostinil with a metered dose inhaler in 2-3 breaths was safe, well tolerated and induced a strong and sustained pulmonary selective vasodilation.

Methods and Patients

A total number of 45 patients with moderate to severe precapillary pulmonary hypertension were enrolled. Patient characteristics were: female to male ratio (f/m)=29/16, age 59±2.3 years, pulmonary artery pressure (PAP) 45±1.8 mmHg, pulmonary vascular resistance (PVR) 743±52 dynes·s·cm⁻⁵, pulmonary artery wedge pressure (PAWP) 8.6±0.5 mmHg, central venous pressure (CVP) 6.4±0.7 mmHg, cardiac output (CO) 4.5±0.2 l/min, central venous oxygen saturation (SvO₂) 62.3±1.2 mmHg (mean±Standard Error of the Mean). Disease etiologies were idiopathic PAH (iPAH) (n=13), PAH other (n=11), chronic thromboembolic pulmonary hypertension (CTEPH) (n=17) and pulmonary fibrosis (n=4). Table 1 presents the patient characteristics of the different groups.

TABLE 1

Patient characteristics of the different treatment groups. Data are given as mean ± Standard Error of the Mean (SEM).				
	Placebo (n = 4)	30 µg TRE (n = 12)	45 µg TRE (n = 9)	60 µg TRE (n = 20)
Age [years]	61 ± 8	53.9 ± 3.9	54.2 ± 5.7	65.5 ± 3.1
PAP [mmHg]	49.5 ± 10.1	45 ± 3.1	54.3 ± 2.8	39.7 ± 2.0
PVR [Dynes]	896 ± 163	597 ± 53.9	1049 ± 107	663 ± 81
CO [l/min]	4.46 ± 0.9	5.2 ± 0.4	3.9 ± 0.4	4.4 ± 0.3
SAP [mmHg]	98 ± 8.1	90.1 ± 3.2	82.8 ± 3.9	86.1 ± 2.0
SaO ₂ [%]	85.3 ± 4.5	90.0 ± 1.1	89.6 ± 1.1	90.6 ± 0.5
SvO ₂ [%]	57.5 ± 3.9	66.0 ± 1.6	59.1 ± 3.4	62.5 ± 1.6

PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; CO = cardiac output; SAP = systemic arterial pressure; SaO₂ = arterial oxygen saturation; SvO₂ = central venous oxygen saturation.

Baseline values were determined 20-30 minutes after placement of the catheter. Heart rate, pulmonary and sys-

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temic blood pressure and cardiac output were measured and blood gases were taken during each pharmacological intervention at defined time points. Pharmacological interventions included the inhalation of 20 ppm nitric oxide (NO) after evaluation of baseline parameters (n=45) and the consecutive inhalation of placebo (n=4), 30 µg SMI-TRE (n=12), 45 µg SMI-TRE (n=9) or 60 µg (n=20) SMI-TRE. Placebo and treprostinil was applied with the Respimat® SMI. For filling of this device with treprostinil sodium, the placebo solution was withdrawn from the device with a syringe and treprostinil solution was injected into the device under sterile conditions. Aerosol quality was controlled before and after refilling of the SMI devices by laser diffractometry, see e.g. Gessler T., Schmehl T., Hoepfer M. M., Rose F., Ghofrani H. A., Olschewski H. et al. Ultrasonic versus jet nebulization of iloprost in severe pulmonary hypertension. Eur. Respir. J. 2001; 17:14-19 incorporated herein in its entirety. The aerosol sizes before (placebo) and after filling (treprostinil) were unchanged. The aerosol particles mass median aerodynamic diameter of treprostinil-aerosol was 4-5 µm, which can be at the upper limit for alveolar deposition. The aerosol volume delivered by one cycle from the SMI was 15 µl. The solution used for aerosol generation was prepared from treprostinil sodium salt using a standard protocol. The SMI was either filled with a concentration of 1000 µg/ml treprostinil sodium (one aerosol puff=15 µg TRE) or with 2000 µg/ml (one puff=30 µg TRE). The different doses were applied as 2 puffs 1000 µg/ml (30 µg), 3 puffs 1000 µg/ml (45 µg) and 2 puffs 2000 µg/ml (60 µg). The placebo was inhaled as 2 puffs from a placebo-SMI. Hemodynamics and gas-exchange parameters were recorded for 120 minutes after TRE inhalation. This study used the Respimat® device, because the implemented "soft mist" technology was well suited for the deposition of such highly active drugs like prostanoids.

The impact of SMI-TRE on ventilation-perfusion matching was assessed in five patients (30 µg TRE, n=2; 45 µg TRE, n=1; 60 µg TRE, n=2) with pre-existing gas exchange problems by use of the multiple inert gas elimination technique (MIGET), see e.g. Wagner P D, Saltzman H A, West J B. Measurement of continuous distributions of ventilation-perfusion ratios: theory. J Appl Physiol. 1974; 36:588-99; Ghofrani H A, Wiedemann R, Rose F, Schermuly R T, Olschewski H, Weissmann N et al. Sildenafil for treatment of lung fibrosis and pulmonary hypertension: a randomised controlled trial. Lancet. 2002; 360:895-900, both incorporated herein in their entirety.

Statistics:

Mean values, standard deviation, standard error of the mean and 95% confidence intervals were calculated. Statistical analysis was done by use of a paired t-test.

Results:

The inhalation of treprostinil sodium from the metered dose inhaler (SMI-TRE) was well tolerated, only mild and transient cough for a maximum of one minute was reported. No systemic side effects like headache, flush, nausea or dizziness were observed.

Two to three breaths of SMI-TRE induced a strong pulmonary vasodilation that outlasted the observation time of 120 minutes (45 and 60 µg). The lower dose of 30 µg TRE induced a somewhat shorter effect on pulmonary vascular resistance; however, the maximal pulmonary vasodilation was comparable. In contrast, placebo inhalation did not induce pulmonary vasodilation. In fact a slight increase in PVR over the time of the right heart catheter investigation could be recorded following placebo inhalation (FIG. 1). The effect of SMI-TRE on systemic vascular resistance and

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pressure was very small and not clinically significant. Cardiac output was significantly increased over the whole observation period, whereas heart rate was rather unchanged. Gas exchange was not influenced by SMI-TRE (FIG. 2). The maximal changes in hemodynamic and gas-exchange parameters compared to baseline values are depicted in Table 2.

TABLE 2

Extremes of the relative changes of hemodynamic and gas exchange parameters compared to baseline after inhalation of Placebo (n = 4), 30 µg treprostinil (n = 12), 45 µg treprostinil (n = 9) and 60 µg treprostinil (n = 20). Highest (max) and lowest (min) values during the observation period are shown. Data are given as percent of baseline values (mean ± SEM).				
	Placebo	30 µg TRE	45 µg TRE	60 µg TRE
PAP (min)	99.4 ± 3.0	83.4 ± 3.2	77.6 ± 6.8	79.5 ± 2.4
PVR (min)	101.4 ± 1.9	84.4 ± 4.4	71.4 ± 8.9	77.5 ± 3.7
CO (max)	99.7 ± 1.1	108.8 ± 3.8	108.6 ± 5.6	103.8 ± 2.0
SVR (min)	104.3 ± 4.3	97.7 ± 4.2	92 ± 3.9	91.3 ± 2.1
SAP (min)	102.7 ± 1.7	97.3 ± 1.9	96.1 ± 1.5	93.6 ± 2.9
HR (max)	105 ± 2.1	106.1 ± 2.9	99.1 ± 2.4	101.1 ± 0.9
SaO2 (min)	98.2 ± 0.4	101 ± 0.3	94.4 ± 1.8	95.8 ± 0.9
SvO2 (max)	104.5 ± 1.4	102.4 ± 1.3	104.5 ± 4.4	102 ± 1.0

PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance; CO = cardiac output; SAP = systemic arterial pressure; HR = heart rate; SaO2 = arterial oxygen saturation; SvO2 = central venous oxygen saturation.

The areas under the curve for PVR were calculated for placebo and the different SMI-TRE doses over the 120 minute observation period (FIG. 3). A dose effect of SMI-TRE with a trend to a more sustained effect with the two highest doses could be observed.

The inhalation of a highly concentrated aerosol can be in theory prone to disturbances of gas exchange because the deposition of even small amounts of aerosol may deliver high doses locally and thereby antagonize the hypoxic pulmonary vasoconstriction in poorly ventilated areas. This would then lead to increased shunt flow or increase of low ventilation/perfusion (V/Q) areas. This question was addressed in five patients with the multiple inert gas elimination technique (MIGET), the gold-standard for intrapulmonary V/Q ratio determination. The MIGET patients were selected for pre-existing gas exchange limitations. Characteristics of these patients were: PAP 54.6±3.2 mmHg, PVR 892±88 dynes, SaO2 91.7±0.5%, SvO2 65.2±1.8%. Etiologies were iPAH (n=1), CTEPH (n=3), pulmonary fibrosis (n=1). The maximal relative reduction of SaO2 after inhalation of SMI-TRE in these patients was -3.8±1.5% compared to baseline values. Shunt flow at baseline, NO-inhalation and 60 minutes after SMI-TRE was 6.4±4.3%, 5.4±3.0% and 8.3±3.4%, respectively (mean±95% confidence interval; FIG. 4).

No significant increase in low V/Q areas or shunt fraction after inhalation of SMI-TRE was observed, in fact the distribution of perfusion was not different to that at baseline and during nitric oxide inhalation. This proves an excellent intrapulmonary selectivity of SMI-TRE, which is also reflected by unchanged arterial oxygen saturation.

Conclusion:

Treprostinil is tolerated at high doses with no systemic side effects. The application of an effective amount of treprostinil in only few or even one single breath was achieved with a highly concentrated treprostinil sodium solution. Treprostinil can be applied by a metered dose inhaler, such as RespiMat® soft mist inhaler.

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Example 2

Investigation of the Effects of Inhaled Treprostinil on Pulmonary Hemodynamics and Gas Exchange in Severe Pulmonary Hypertension

This study investigated the effects of inhaled treprostinil on pulmonary vascular resistance in severe pulmonary hypertension and addressed systemic effects and gas exchange as well as tolerability and efficacy of high doses of treprostinil given in short time. A total of 123 patients with a mean pulmonary artery pressure of about 50 mmHg were investigated in three separate randomized studies. Inhaled treprostinil exerted potent sustained pulmonary vasodilation with excellent tolerability and could be safely applied in a few breaths or even one breath.

Summary:

Three different studies were conducted on a total of 123 patients by means of right heart catheterization: i) a randomized crossover-design study (44 patients), ii) a dose escalation study (31 patients) and iii) a study of reduction of inhalation time while keeping the dose fixed (48 patients). The primary endpoint was the change in pulmonary vascular resistance (PVR).

The mean pulmonary artery pressure of the enrolled patients was about 50 mmHg. Hemodynamics and patient characteristics were similar in all studies. In study i) TRE and Iloprost (ILO), at an inhaled dose of 7.5 µg, displayed comparable PVR decrease, with a significantly different time course (p<0.001), TRE exhibiting a more sustained effect on PVR (p<0.0001) and less systemic side effects. In study ii) placebo, 30 µg, 60 µg, 90 µg or 120 µg TRE were applied with drug effects being observed for 3 hours after inhalation. A near-maximal acute PVR decrease was observed at 30 µg TRE. In study iii) TRE was inhaled with a pulsed ultrasonic nebulizer, mimicking a metered dose inhaler. 15 µg TRE was inhaled with 18 pulses (TRE concentration 100 µg/ml), 9 pulses (200 µg/ml), 3 pulses (600 µg/ml), 2 pulses (1000 µg/ml) or 1 pulse (2000 µg/ml), each mode achieving comparable, sustained pulmonary vasodilation.

Inhaled treprostinil exerts sustained pulmonary vasodilation with excellent tolerability at doses, which may be inhaled in a few or even one breath. Inhaled treprostinil is advantageous to inhaled iloprost in terms of duration of effect and systemic side effects. Inhaled treprostinil is well tolerated in concentrations up to 2000 mg/ml (bringing down inhalation time to a single breath) and in high doses (up to 90 µg).

Methods:

All inhalations were performed with the OPTINEB® ultrasonic nebulizer (NebuteC, Elsenfeld, Germany).

Study i) was a randomized, open-label, single-blind crossover study. The primary objective was to compare the acute hemodynamic effects and the systemic side effects of inhaled treprostinil with inhaled iloprost at comparable doses. A total number of 44 patients with moderate to severe precapillary pulmonary hypertension were enrolled. Patient characteristics and hemodynamic as well as gas exchange parameters are outlined in Table 3.

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TABLE 3

Patient characteristics, hemodynamic parameters and gas exchange values at baseline, before challenge with inhalative prostanoids.												
N	Age	Gender f/m	Etiology i/o/t/f	PAP [mmHg]	PVR [dyn * s * cm ⁻⁵]	SAP [mmHg]	CVP [mmHg]	PAWP [mmHg]	CO [l/min]	SaO ₂ [%]	SvO ₂ [%]	
1a	14	55.1 ± 4.8	11/3	4/4/2/4	53.8 ± 3.1	911 ± 102	95.4 ± 3.6	7.4 ± 1	8.0 ± 0.8	4.3 ± 0.4	93.8 ± 2	63.9 ± 2.4
1b	14	54.1 ± 3.3	10/4	1/6/5/2	47.4 ± 3.8	716 ± 80	90.6 ± 3.3	5.9 ± 1.4	6.4 ± 0.7	4.7 ± 0.4	92 ± 1	64.4 ± 2.3
1c	16	56 ± 2.9	7/9	6/3/6/1	47.5 ± 4.5	777 ± 102	92 ± 4.5	8.3 ± 1.4	8.6 ± 1.4	4.4 ± 0.5	91.4 ± 0.9	59.8 ± 2.6
2a	8	60.8 ± 4	4/4	2/2/3/1	51.9 ± 4.9	849 ± 152	95.9 ± 4.8	7.6 ± 1.4	11.1 ± 1.7	4.4 ± 0.6	89.6 ± 2.8	60.1 ± 2.8
2b	8	52.8 ± 6.6	6/2	1/3/3/1	49 ± 4	902 ± 189	92.4 ± 2.4	4.8 ± 1.1	7.2 ± 1.3	4.0 ± 0.4	92.4 ± 2.4	62.5 ± 1.7
2c	6	56.8 ± 5.9	4/2	0/2/2/2	44.2 ± 3.5	856 ± 123	96.3 ± 3.9	5 ± 1.1	6 ± 1	3.8 ± 0.3	92.8 ± 1.5	63.6 ± 1.8
2d	6	51.2 ± 3.8	4/2	2/2/2/0	55.5 ± 4.9	940 ± 110	91.2 ± 8.1	11.2 ± 1.2	10 ± 0.7	3.9 ± 0.4	92 ± 1.9	62 ± 5.8
2e	3	57.3 ± 9.1	1/2	0/1/0/2	45.3 ± 5.2	769 ± 267	99 ± 3.2	5 ± 2.1	9 ± 0.6	4.5 ± 0.6	94.2 ± 1.3	66.3 ± 1.5
3a	6	52.7 ± 6.6	4/2	2/4/0/0	53.8 ± 6.7	928 ± 145	92.7 ± 7.9	8.7 ± 2.7	8.8 ± 1.3	4.2 ± 0.6	90.4 ± 2.8	64.8 ± 4.3
3b	6	58.3 ± 3.5	4/2	3/1/1/1	54.2 ± 6.1	808 ± 156	94.3 ± 2.8	7 ± 1.4	10 ± 1.3	5 ± 0.7	91.9 ± 0.7	63.5 ± 2.9
3c	21	57.4 ± 5.6	8/3	7/7/6/1	46.1 ± 2.5	900 ± 99	88 ± 2.8	9 ± 1.4	9.2 ± 0.5	3.7 ± 0.3	91.7 ± 0.5	59.7 ± 2
3d	7	55.6 ± 5.8	3/4	0/4/3/0	53.1 ± 7.1	732 ± 123	91.4 ± 5.6	7.9 ± 3.1	8.6 ± 1.3	5 ± 0.4	90.7 ± 1.4	61.3 ± 3.7
3e	8	59 ± 5.2	7/1	0/4/4/0	45.1 ± 3.9	733 ± 114	92.8 ± 6.8	4.6 ± 0.8	8.1 ± 1.1	4.3 ± 0.2	90.7 ± 0.8	66.3 ± 2.8

Group 1 corresponds to study i); randomized crossover study comparing inhaled iloprost (ILO) and inhaled treprostinil (TRE).

a = 7.5 g ILO vs. 7.5 µg TRE,

b = 7.5 g ILO vs. 15 µg TRE (6 min inhalation time),

c = 7.5 g ILO vs. 15 µg TRE (3 min inhalation time).

Group 2 corresponds to study ii); evaluation of maximal tolerated dose of TRE.

a = placebo inhalation,

b = 30 µg TRE,

c = 60 µg TRE,

d = 90 µg TRE,

e = 120 µg TRE.

Group 3 corresponds to study iii); reduction of inhalation time by increase of TRE concentration, aiming at a total inhaled dose of 15 µg.

a = 18 pulses of 100 µg/ml TRE,

b = 9 pulses of 200 µg/ml TRE,

c = 3 pulses of 600 µg/ml TRE,

d = 2 pulses of 1000 µg/ml TRE,

e = 1 pulse 2000 µg/ml TRE.

Etiology of pulmonary hypertension was classified as idiopathic PAH (i), PAH of other causes (o), chronic thromboembolic PH (t), and pulmonary fibrosis (f).

Each patient inhaled both iloprost and treprostinil on the same day during right heart catheter investigation; the drugs were administered consecutively with a one hour interval between the drug applications. One half of the study patients initially inhaled treprostinil and then inhaled iloprost (n=22), while the other half initially inhaled iloprost and then inhaled treprostinil (n=22). Patients were randomized to one of the two groups and blinded as to the study drugs. Drug effects were monitored for 60 minutes after each inhalation. Iloprost was inhaled at 4 µg/ml (6 min inhalation time; n=44) and treprostinil was inhaled at a concentration of 4 µg/ml (6 min inhalation; n=14), 8 µg/ml (6 min inhalation; n=14) or 16 µg/ml (3 min inhalation; n=16). Based on previous biophysical characterization of the ultrasonic device with iloprost- and treprostinil-solution, this corresponds to a total inhaled dose of 7.5 µg iloprost and treprostinil (4 µg/ml) and 15 µg treprostinil (8 µg/ml and 16 µg/ml), respectively.

Study ii) was a randomized, open-label, single blind, placebo controlled study. The primary objectives were to describe the pharmacodynamic and pharmacokinetic effects of inhaled treprostinil at a well tolerated dose (30 µg) and to explore the highest tolerated single dose. A total number of 31 patients inhaled either placebo or treprostinil; each patient received one inhalation. The first 16 patients were randomized to 30 µg TRE (16 µg/ml, n=8) or placebo (stock solution in a concentration corresponding to TRE 16 µg/ml). Subsequent patients received 60 µg TRE (32 µg/ml; n=6), 90 µg TRE (48 µg/ml; n=6) and 120 µg TRE (64 µg/ml; n=3). Inhalation time was 6 minutes in all groups. Hemodynamics and gas-exchange as well as arterial treprostinil concentrations were recorded for 180 minutes.

Study iii) was a randomized, open-label, single blind study. The primary objective was to explore the shortest possible inhalation time for a 15 µg dose of inhaled trepro-

stinil. A total of 48 patients inhaled one dose of TRE during right heart catheter investigation. The drug was applied in 18, 9, 3, 2 or 1 breaths. The aerosol was generated by a pulsed ultrasonic nebulizer (OPTINEB®, Nebutech, Elsenfeld, Germany) in cycles consisting of 2 seconds aerosol production (pulse) and 4 seconds pause. The device included an opto-acoustical trigger for the patient to synchronize the inspiration to the end of the aerosol pulse, thereby providing exact dosage. The TRE dose of 15 µg was either generated during 18 cycles (OPTINEB® filled with 100 µg/ml TRE, n=6), 9 cycles (200 µg/ml TRE, n=6), 3 cycles (600 µg/ml TRE, n=21), 2 cycles (1000 µg/ml TRE, n=7) or 1 cycle (2000 µg/ml TRE, n=8). Hemodynamics and gas exchange were recorded for 120-180 minutes.

Treprostinil plasma concentrations were assessed in study ii) at 10, 15, 30, 60 and 120 minutes after inhalation. Treprostinil quantification was done by Alta Analytical Laboratory (El Dorado Hills, Calif., USA) with a validated liquid chromatography atmospheric-pressure ionization tandem mass spectrometry as previously described Wade M., et al. J. Clin. Pharmacol. 2004; 44:503-9. Mixed venous blood was drawn at the depicted time points (FIG. 11) after inhalation, centrifuged and the plasma frozen at -80° C. until temperature controlled shipping on dry ice.

Statistics:

For statistical analysis of study i) the repeated PVR measurements after inhaled iloprost and treprostinil were subjected to a three-factorial analysis of variance (ANOVA; factors: time (A), drug (B), treprostinil concentration (C)) to avoid multiple testing. The time to maximum PVR decrease after inhalation of iloprost versus treprostinil was compared by paired t-test. Area under the curve (AUC) was calculated from start of inhalation until 60 min after inhalation. Means, standard error of the mean (SEM) and 95% confidence

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intervals were calculated. For study ii) and iii) areas between curves (ABC) were calculated between placebo inhalation (study ii) and the respective treprostinil inhalation until 180 min (study ii) and 120 min (study iii) after end of inhalation.

Results:

The inhalation of iloprost as well as treprostinil in study i) resulted in a rapid decrease in PVR and PAP (FIG. 5-7). No significant differences were observed for the areas under the curve (AUC) of PVR decrease after inhalation of 7.5 µg TRE in 6 minutes (AUC $-12.6 \pm 7.0\%$), 15 µg TRE in 6 minutes (AUC $-13.3 \pm 3.2\%$) and 15 µg TRE in 3 minutes (AUC $-13.6 \pm 4.3\%$). The AUC for PVR after the inhalation of 7.5 µg iloprost in 6 minutes was $-7.7 \pm 3.7\%$ (mean $\pm 95\%$ confidence interval). An overview of the pooled data of treprostinil inhalation as compared to iloprost inhalation is given in FIG. 7. The maximum effect of iloprost and treprostinil on PVR was comparable but this effect was reached significantly later after treprostinil inhalation (18 ± 2 min) compared to iloprost (8 ± 1 min; mean \pm SEM, $p < 0.0001$) and lasted considerably longer (after 60 min, PVR values in the treprostinil group had not yet returned to baseline). The increase in cardiac output was less acute but prolonged after treprostinil inhalation. Systemic arterial pressure (SAP) was unaffected by treprostinil inhalation, whereas a transient decrease was observed after iloprost inhalation. Iloprost and treprostinil did not affect gas exchange. Three-factorial ANOVA for PVR demonstrated a significant difference between repeated measurements after inhalation ($p_{(A)} < 0.0001$), no significant difference between drugs ($p_B = 0.1$), no difference between treprostinil concentrations ($p_{(C)} = 0.74$) and a significant drug \times time interaction ($p_{(A \times B)} < 0.0001$). This translates into a significant effect of both drugs on PVR with comparable drug potency but a prolonged drug effect of treprostinil compared to iloprost.

In this study the occasionally observed mild side effects of iloprost inhalation at the given dose (transient flush, headache) were not observed with inhaled treprostinil. Bad taste was reported by most of the patients after inhalation of TRE. This was later found to be attributable to the metacresol preservative contained in the treprostinil solution.

In study ii) pharmacodynamics of inhaled placebo or treprostinil were observed for 180 minutes. Placebo inhalation was followed by a gradual increase in PVR over the entire observation time. Due to reduced patient numbers in the 120 µg TRE group (because of side effects, see below), the hemodynamic values for this group were not included in the graphs of this study (FIG. 8-9). All TRE doses lead to comparable maximal decreases of PVR to $76.5 \pm 4.7\%$ (30 µg), $73.7 \pm 5.8\%$ (60 µg), $73.3 \pm 4.3\%$ (90 µg) and $65.4 \pm 4.1\%$ (120 µg) of baseline values. An extended duration of pulmonary vasodilation was noted, surpassing the 3 hour observation period for the 60 µg and 90 µg (and 120 µg) TRE doses, whereas in the 30 µg dose group the hemodynamic changes had just returned to baseline within this period. Even at the highest doses, TRE had only minor effects on systemic arterial pressure (FIG. 8). Cardiac output was increased to a maximum of $106.8 \pm 3.2\%$ (30 µg), $122.9 \pm 4.3\%$ (60 µg), $114.3 \pm 4.8\%$ (90 µg) and $111.3 \pm 3.9\%$ (120 µg TRE). The areas between the response curves after placebo versus TRE inhalation were calculated for PVR, PAP, SVR and SAP (FIG. 9). Areas between the curves for PVR were not significantly different for 30 µg, 60 µg and 90 µg TRE, a nearly maximal effect on PVR was already observed with 30 µg TRE. Effects on PAP and SAP were small and did not show a dose-response relationship. Gas exchange was not affected at doses up to 90 µg TRE, but

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arterial oxygen saturation was significantly decreased at a dose of 120 µg TRE in all 3 patients. Further dose increments were omitted due to this side effect and severe headache in one patient.

Again, bad taste of the TRE aerosol was reported by most patients. Other side effects were flushing ($n=1$; 30 µg TRE), mild transient cough ($n=3$; 60 µg TRE), mild transient bronchoconstriction that resolved after one inhalation of fenoterol ($n=1$; 30 µg TRE), moderate bronchoconstriction that resolved after one inhalation of fenoterol ($n=1$; 120 µg TRE), and severe headache ($n=1$; 120 µg TRE). The bad taste, the bronchoconstriction and the drop in SaO₂ was attributed to metacresol in the original TRE solution. With the use of a metacresol-free solution of TRE (University Hospital Giessen, Germany; produced according to the manufacturer's protocol) in the following study, these side effects did no longer occur.

Study iii) was performed with metacresol-free TRE solution, having no specific taste and smell. A total of 48 patients were enrolled. This study aimed at the reduction of inhalation time and aerosol volume needed for pulmonary drug delivery. A modified OPTINEB® inhalation device was programmed to produce a constant amount of aerosol during repeatable pulses of aerosol generation. With this device, treprostinil could be safely utilized up to a concentration of 2000 µg/ml without considerable side effects. No relationship of number or type of side effects to TRE concentration was observed. Reported side effects were mild transient cough ($n=6$), mild headache ($n=2$) and mild jaw pain ($n=1$).

The reduction of PVR and PAP was comparable between all groups (FIG. 10). TRE inhalation reduced PVR to $76.3 \pm 5.6\%$ (18 pulses, 100 µg/ml), $72.9 \pm 4.9\%$ (9 pulses, 200 µg/ml), $71.2 \pm 6.0\%$ (3 pulses, 600 µg/ml), $77.4 \pm 4.5\%$ (2 pulses, 1000 µg/ml) and $80.3 \pm 5.2\%$ (1 pulse, 2000 µg/ml). PAP was reduced to $84.2 \pm 4.5\%$ (18 pulses, 100 µg/ml), $84.2 \pm 4.1\%$ (9 pulses, 200 µg/ml), $81.1 \pm 4.1\%$ (3 pulses, 600 µg/ml), $86 \pm 4\%$ (2 pulses, 1000 µg/ml) and $88 \pm 5.4\%$ (1 pulse, 2000 µg/ml). Cardiac output was moderately increased in all groups, whereas systemic arterial pressure was not significantly affected.

The areas between the curves (ABC) for changes in hemodynamic and gas-exchange parameters after inhalation of 15 µg TRE versus placebo were calculated for an observation time of 120 minutes (FIG. 11). The ABC for both PVR and PAP was comparable between all groups.

Pharmacokinetic results from study ii): Peak plasma concentrations of treprostinil were found 10-15 minutes after inhalation. Maximal treprostinil plasma concentrations (C_{max}) for the 30 µg, 60 µg, 90 µg and 120 µg doses were 0.65 ± 0.28 ng/ml ($n=4$), 1.59 ± 0.17 ng/ml ($n=4$), 1.74 ng/ml ($n=1$) and 3.51 ± 1.04 ng/ml ($n=2$), respectively (mean \pm SEM; FIG. 12).

Discussion:

These studies investigated whether i) the acute effects of inhaled treprostinil would be comparable to or possibly advantageous over inhaled iloprost in pulmonary hypertensive patients, ii) the inhaled prostanoid dose might be increased without substantial local or systemic side effects, and iii) if the time of inhalation, which is 6-12 minutes for iloprost, could be reduced significantly by increasing the concentration of treprostinil aerosol.

The patient population in these studies included different forms of precapillary pulmonary hypertension. All these patients had a need for therapy of pulmonary hypertension and reflected the typical population of a pulmonary hyper-

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tension center. No major differences in patient characteristics or hemodynamic baseline values existed between the different groups (table 3).

In study i) it was shown that the inhalation of treprostinil and iloprost in similar doses resulted in a comparable maximum pulmonary vasodilatory effect. However, marked differences in the response profile were noted. The onset of the pulmonary vasodilatory effect of inhaled treprostinil was delayed compared to iloprost, but lasted considerably longer, with the PVR decrease continuing beyond the one-hour observation period. Although the average dose of treprostinil was higher than the iloprost dose, no systemic effects were noted after treprostinil inhalation, whereas flush and transient SAP decrease, accompanied by more prominent cardiac output increase, occurred after iloprost inhalation. Such side effects were more prominent than in previous studies with inhaled iloprost. This may have been caused by the fact that the iloprost dose used in this study was 50% higher than the recommended single inhalation dose (5 µg) and that the preceding treprostinil inhalation may have added to the systemic side effects caused by the iloprost inhalation. Surprisingly, with TRE there was no such systemic side effect, although the average effect on PVR was as potent as with iloprost.

This study used a cross-over design in order to minimize the effects of inter-individual differences in response to prostanooids. The short observation period of 1 hour was used to avoid an uncomfortably long catheter investigation. As a study limitation, the short observation interval may have caused carryover effects of the first to the second period as suggested by FIG. 5. However, this still allowed for the interpretation of the study, that both drugs are potent pulmonary vasodilators and that treprostinil effects are significantly sustained compared to the iloprost effects.

The longer duration of action and the virtual absence of side effects (except the bitter taste of treprostinil aerosol, later attributed to metacresol) encouraged increasing the applied treprostinil dose in study ii). Observation time was extended to 3 hours to obtain precise pharmacodynamic data. Inhaled treprostinil resulted in a strong pulmonary vasodilation that outlasted the observation time of 3 hours when compared to placebo inhalation. Surprisingly, inhaled treprostinil was tolerated in doses up to 90 µg.

Study iii) successfully demonstrated that the inhalation time could be reduced to literally one single breath of 2000 µg/ml treprostinil solution, thereby applying a dose of 15 µg.

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This drug administration with a single breath induced pulmonary vasodilation for longer than 3 hours compared to placebo inhalation. Side effects were minor, of low frequency and not related to drug concentration. It was a surprising finding that such high concentrations of treprostinil were so well tolerated.

Conclusion:

Inhaled treprostinil can be applied in high doses (up to 90 µg) with a minimal inhalation time. Inhaled treprostinil exerts high pulmonary selectivity and leads to a long-lasting pulmonary vasodilation.

Although the foregoing refers to particular preferred embodiments, it will be understood that the present invention is not so limited. It will occur to those of ordinary skill in the art that various modifications may be made to the disclosed embodiments and that such modifications are intended to be within the scope of the present invention.

All of the publications, patent applications and patents cited in this specification are incorporated herein by reference in their entirety.

What is claimed is:

1. A method of treating pulmonary hypertension comprising administering by inhalation to a human suffering from pulmonary hypertension a therapeutically effective single event dose of a formulation comprising treprostinil or a pharmaceutically acceptable salt thereof with an inhalation device, wherein the therapeutically effective single event dose comprises from 15 micrograms to 90 micrograms of treprostinil or a pharmaceutically acceptable salt thereof delivered in 1 to 3 breaths.

2. The method of claim 1, wherein the inhalation device is a soft mist inhaler.

3. The method of claim 1, wherein the inhalation device is a pulsed ultrasonic nebulizer.

4. The method of claim 1, wherein the inhalation device is a dry powder inhaler.

5. The method of claim 1, wherein the inhalation device is a pressurized metered dose inhaler.

6. The method of claim 4, wherein the formulation is a powder.

7. The method of claim 6, wherein the powder comprises particles less than 5 micrometers in diameter.

8. The method of claim 1, wherein the formulation contains no metacresol.

* * * * *

EXHIBIT 17

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pulse

[noun](#) (1)

\ 'pʌls \

Definition of *pulse*

(Entry 1 of 3)

1a : the palpable beat resulting from such pulse as detected in a superficial artery also : the number of individual beats in a specified time period (such as one minute) a resting pulse of 70
b : the regular expansion of an artery caused by the ejection of blood into the arterial system by the contractions of the heart
2a : rhythmical beating, vibrating, or sounding
b : [beat](#), [throb](#)
3a : underlying sentiment or opinion or an indication of it
b : [vitality](#)
4a : a transient variation of a quantity (such as electric current or voltage) whose value is normally constant
b(1) : an electromagnetic wave or modulation thereof of brief duration
(2) : a brief disturbance of pressure in a medium especially : a sound wave or short train of sound waves
5 : a dose of a substance especially when applied over a short period of time pulses of intravenous methylprednisolone

pulse

[verb](#)

pulsed; pulsing

Definition of *pulse* (Entry 2 of 3)

[intransitive verb](#)

: to exhibit a pulse or [pulsation](#) : [throb](#)

[transitive verb](#)

1 : to drive by or as if by a pulsation
2 : to cause to [pulsate](#)
3a : to produce or modulate (something, such as electromagnetic waves) in the form of [pulses](#) *pulsed* waves
b : to cause (an apparatus) to produce pulses

pulse

[noun \(2\)](#)

Definition of *pulse* (Entry 3 of 3)

: the edible seeds of various crops (such as peas, beans, or lentils) of the legume family also : a plant yielding pulse

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Verb

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Synonyms: Verb

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Examples of *pulse* in a Sentence

Verb

He could feel the blood *pulsing* through his veins. Dance music *pulsed* from the speakers.

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First Known Use of *pulse*

Noun (1)

14th century, in the meaning defined at [sense 1b](#)

Verb

15th century, in the meaning defined at [intransitive sense](#)

Noun (2)

13th century, in the meaning defined [above](#)

History and Etymology for *pulse*

Noun (1)

Middle English *puls*, from Anglo-French, from Latin *pulsus*, literally, beating, from *pellere* to drive, push, beat — more at [felt](#)

Noun (2)

Middle English *puls*, probably from Anglo-French *puiiz* gruel, from Latin *pult-*, *puls*, probably from Greek *poltos*

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pulse

[verb](#)

English Language Learners Definition of *pulse*

- : to move with strong, regular beats
- : to produce a strong, regular beat
- : to be filled with activity or a feeling

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pulse

[noun](#)

\ 'pʌls 

Kids Definition of *pulse*

- 1 : a strong regular beating or throbbing the rhythmic *pulse* of the music
- 2 : the beat resulting from the regular widening of an artery in the body as blood flows through it Feel your wrist for a *pulse*.

pulse

[noun](#)

\ 'pʌls 

Medical Definition of *pulse*

(Entry 1 of 2)

1a : a regularly recurrent wave of distension in arteries that results from the progress through an artery of blood injected into the arterial system at each contraction of the ventricles of the heart

b : the palpable beat resulting from such pulse as detected in a superficial artery (as the radial artery) a very soft pulse also : the number of such beats in a specified period of time (as one minute) a resting pulse of 70

2 : [pulsation](#)

3a : a transient variation of a quantity (as electric current or voltage) whose value is normally constant —often used of current variations produced artificially and repeated either with a regular period or according to some code

b : an electromagnetic wave or modulation thereof having brief duration

c : a brief disturbance transmitted through a medium

4 : a dose of a substance especially when applied over a short period of time therapy with pulses of intravenous methylprednisolone

pulse

[verb](#)

pulsed; pulsing

Medical Definition of *pulse* (Entry 2 of 2)

[intransitive verb](#)

: to exhibit a pulse or [pulsation](#)

[transitive verb](#)

1 : to cause to [pulsate](#)

2a : to produce or modulate (as electromagnetic waves) in the form of [pulses](#) *pulsed* waves

b : to cause (an apparatus) to produce pulses

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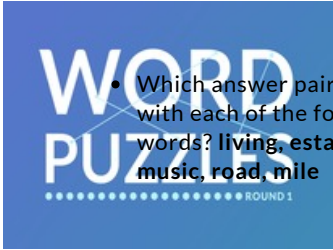
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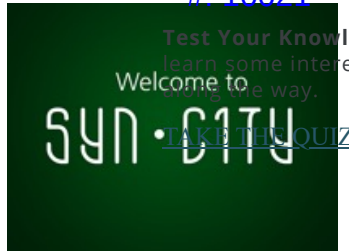
- Which answer pairs best with each of the following words? living, estate, club, music, road, mile

- | | |
|----------------|--------------|
| <u>country</u> | <u>eight</u> |
| <u>rural</u> | <u>dance</u> |



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Text messages reveal t...
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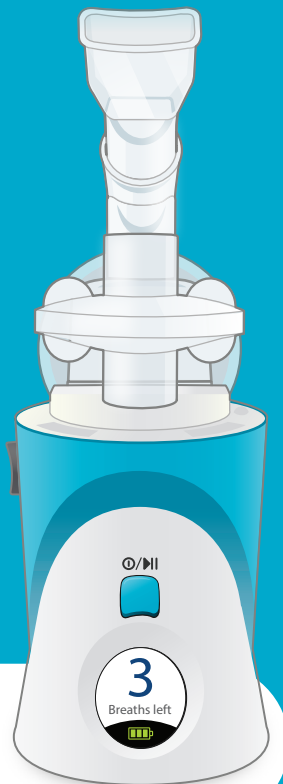
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EXHIBIT 18

TYVASO[®] ***INHALATION SYSTEM***

Instructions for Use Manual



Overview

**Program
before use**

**Prepare
and use**

**Clean
and store**

**Help and
more info**

Contents

#: 10028

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Overview of your TYVASO Inhalation System

Section overview

This section introduces you to your TYVASO Inhalation System and provides important safety information about using your system.

What you will need:

- ▶ A clean place to review these instructions
- ▶ TYVASO Inhalation System to refer to while reading instructions

What is covered in this section:

A: Introduction	6
B: Safety and general instructions	8
C: Buttons, indicators, and markings	10
D: Inhalation device display screens	16

Important:

Do not start treatment with TYVASO until you have been trained to use the TYVASO Inhalation System. Make sure you understand all of the directions. Always ask your doctor or specialty pharmacy provider if you have any questions or are unsure of anything you are taught.

A: Introduction

Your doctor has prescribed TYVASO® (treprostinil) Inhalation Solution. Please see the accompanying Patient Information for important safety information on TYVASO.

TYVASO is a prescription medicine used in adults to treat pulmonary arterial hypertension (PAH; WHO Group 1) and pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3), which are diseases causing high blood pressure in the arteries of your lungs. TYVASO can improve exercise ability. The effects decrease over 4 hours; treatment timing can be adjusted for planned activities.

TYVASO is breathed in (inhaled) using the TYVASO Inhalation System, which consists of the inhalation device and its accessories.

This Instructions for Use manual for the TYVASO Inhalation System provides important safety information. It is important that you read these instructions and the TYVASO Patient Information before setting up and using the TYVASO Inhalation System. If you have any questions, talk to your doctor or specialty pharmacy provider.

Before beginning treatment with TYVASO, you will receive either a Patient Starter Kit containing a 28-day supply of TYVASO or an Institutional Starter Kit containing a 4-day supply of medication.

Both kits include 2 complete inhalation devices (all accessories and supplies included). When you refill your prescription for TYVASO each month, you will receive a Refill Kit that contains a 28-day supply of TYVASO and new accessories. You will receive replacement devices every 2 years from your date of receipt of the TYVASO Inhalation System.

⚠ CAUTION: Federal law restricts this device to sale by or on the order of a physician, or other licensed practitioner.

Important:

- Keep this Instructions for Use manual in a safe place where you can easily get to it for reference. For example, store the booklet in the TYVASO Inhalation System carrying case, along with your other supplies.
- TYVASO Inhalation System is intended solely for the delivery of TYVASO (treprostinil) Inhalation Solution. TYVASO is for administration only with the TYVASO Inhalation System.

B: Safety and general instructions

The TYVASO Inhalation System should be handled carefully. Take the following precautions and follow all instructions in this document to avoid injury and ensure proper use:

Delivering treatments:

- Read the instructions carefully and completely to prevent damage to your TYVASO Inhalation System and help you get the best results.
- This device should only be used on the order of your doctor or licensed healthcare practitioner.
- Conduct only the number of treatment sessions and inhalations you have been prescribed.
- Ensure the breath counter is correctly programmed prior to beginning a treatment (see page 22).
- Turn off the device when not in use.
- Do not use the device with an anesthetic breathing system or ventilator breathing system.
- Use only the supplies provided in the Starter Kit and Monthly Refill Kit for correct device function.

Handling the device:

- Do not peel or remove the labels from the device.
- Do not drop the device.
- The device does not include internal, replaceable parts. Do not attempt to open the device, modify the device, or remove device labeling.

Your environment:

- Do not leave the device alone with a small child.
- Do not immerse the device in water or other liquids, or place in dishwasher.
- Do not place any system components in a microwave, conventional oven, or dishwasher.
- Do not use the device near flammable liquids and materials or heated surfaces.
- Do not place the device or use the device in the presence of strong electric or magnetic fields (e.g., microwave oven, magnetic imaging equipment).
- Wireless communications equipment (e.g., cell phone) can affect operation of the device and should be kept at least a distance of 3.3 meters (about 11 feet) away while using the device.
- If the device performance is affected by exposure to any conditions listed here, see the Troubleshooting section, or contact your healthcare provider or specialty pharmacy provider.

C: Buttons, indicators, and markings

Inhalation device

Inhalation indicator lights

Lights on top of device flash green when you should inhale.

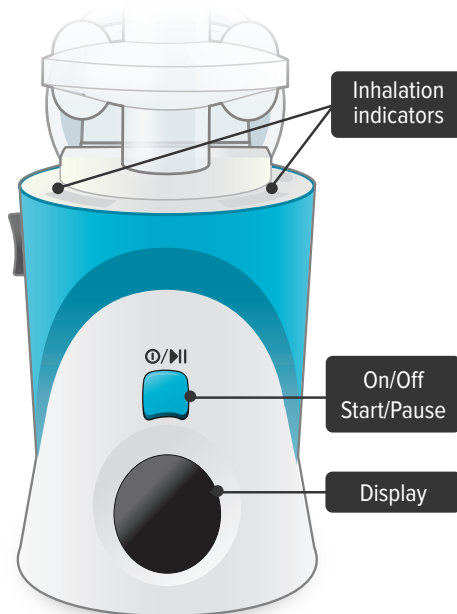
⏻/▶ On/Off, Start/Pause (blue) button

Press and **hold** to power device on or off.

Once device is on, press **and immediately release** (do not hold down) to start or pause treatment.

Device Display

Provides instructions and device information.



Front

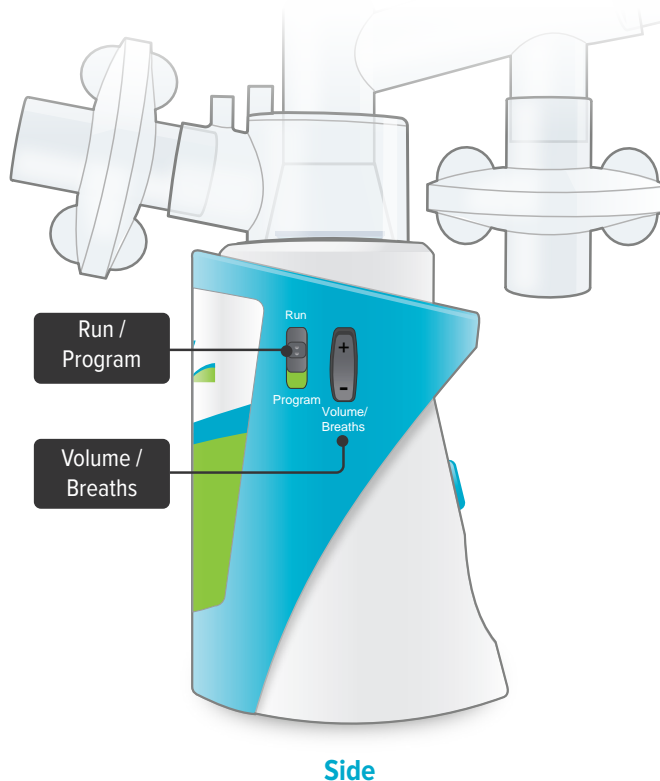
Run / Program switch

Slide up to Run mode when you are ready to deliver your dose. Slide down to Program mode to program the number of breaths for your dose.

Volume / Breaths toggle button

When set to Run mode, push **+** to increase beeping volume, or push **-** to decrease beeping volume.

When set to Program mode, push **+** to increase the number of breaths, or push **-** to decrease the number of breaths required for each dose.



Inhalation device (continued)

Power status light

● Lights green when power is connected and battery is charging.

Power port

Port for plugging into a power source using the AC wall plug.



Additional device markings



Manufacturer. Indicates the medical device manufacturer.
(Symbol 5.1.1 of ANSI/AAMI/ISO 15223-1: 2012 Medical devices - symbols to be used with medical devices labels, labeling, and information to be supplied - part 1: general requirements)



Equipment should not be disposed of in the trash.
(Figure 1 of BS EN 50419:2006 - Marking of Electrical and Electronic Equipment in accordance with Article 11(2) of Directive 2002/96/EC (WEEE))



Catalogue number. Indicates the manufacturer's catalogue number so that the medical device can be identified. (Symbol 5.1.6 of ANSI/AAMI/ISO 15223-1: 2012 Medical devices - symbols to be used with medical devices labels, labeling, and information to be supplied - part 1: general requirements)



Serial number. Indicates the manufacturer's serial number so that a specific medical device can be identified. (Symbol 5.1.7 of ANSI/AAMI/ISO 15223-1: 2012 Medical devices - symbols to be used with medical devices labels, labeling, and information to be supplied - part 1: general requirements)



Consult instructions for use. Please read the accompanying instructions and labels for important information regarding the TYVASO Inhalation System. (Symbol 5.4.3 of ANSI/AAMI/ISO 15223-1: 2012 Medical devices - symbols to be used with medical devices labels, labeling, and information to be supplied - part 1: general requirements)



The TYVASO Inhalation System has a Type BF Applied part. Type BF Applied parts comply with specific requirements to provide protection against shock and are not suitable for direct cardiac applications. (Symbol 5333 of IEC 60417 Database Snapshot - Graphical symbols for use on equipment)



The TYVASO Inhalation System requires a 14V DC power supply. Use only the power supply intended for the TYVASO Inhalation System. (Direct Current, Symbol 5031 of IEC 60417 Database Snapshot - Graphical symbols for use on equipment)



The TYVASO Inhalation System complies with the requirements of Protection Class II. Class II equipment provides additional precautions, over and above basic insulation, to provide protection against electric shock. (Class II equipment, Symbol 5172 of IEC 60417 Database Snapshot - Graphical symbols for use on equipment)

IP22

The TYVASO Inhalation Device provides level 2 solid particle protection and level 2 liquid ingress protection per IEC 60529 specifications.

Rx Only

The TYVASO Inhalation System should only be used on the order of your doctor or licensed healthcare provider. (Symbol statement as provided under 21 CFR 801.109(b)(1))



Power stand by. Indicates the control for powering on and off the TYVASO Inhalation System. (“On” / “Off”, Symbol 5010 of IEC 60417 Database Snapshot - Graphical symbols for use on equipment)

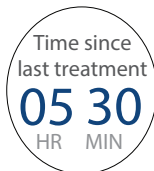


Start/Pause. Indicates the control for starting a treatment session once the device is powered on, and for pausing a treatment once a treatment session has started. (Play and Pause, Symbols 5107B and 5111B, respectively, of IEC 60417 Database Snapshot - Graphical symbols for use on equipment)

D: Inhalation device display screens



Splash screen
 Device name and software version



Last Treatment
 Time since your last treatment



Program Breaths
 Number of breaths set in Program mode



Adjust Volume
 Audio volume level set in Run mode



Breaths Left
 Number of breaths left in a current dose



Exhale
 Prompt to exhale during a dose



Inhale
 Prompt to inhale during a dose



Done
 Treatment session is complete



Pause

You have paused a treatment session



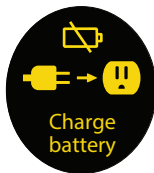
Call Support

Device is not working, call your specialty pharmacy provider for support



Add Water

Wrong or missing fluid in water chamber



Charge Battery

Battery not charged enough to deliver treatment



Battery full



Battery more than half full



Battery less than half full



Battery almost empty



Battery charging



Audio off (volume all the way down)

Status icons

Icons that might appear at bottom of the screen

Program
before use

Programming your TYVASO Inhalation System before use

*Program
before use*

Section overview

This section provides instructions for charging your device, setting your dose, and adjusting the device's audio volume before you use the device for a treatment.

What you will need:

- ▶ A clean place to work with the device
- ▶ TYVASO Inhalation Device
- ▶ The number of breaths your doctor prescribed for each dose

What is covered in this section:

A: Charging device before use	20
B: Setting your prescribed dose	22
C: Adjusting device's audio volume	24

Important:

Do not start treatment with TYVASO until you have been trained to use the TYVASO Inhalation System. Make sure you understand all of the directions. Always ask your doctor or specialty pharmacy provider if you have any questions or are unsure of anything you are taught.

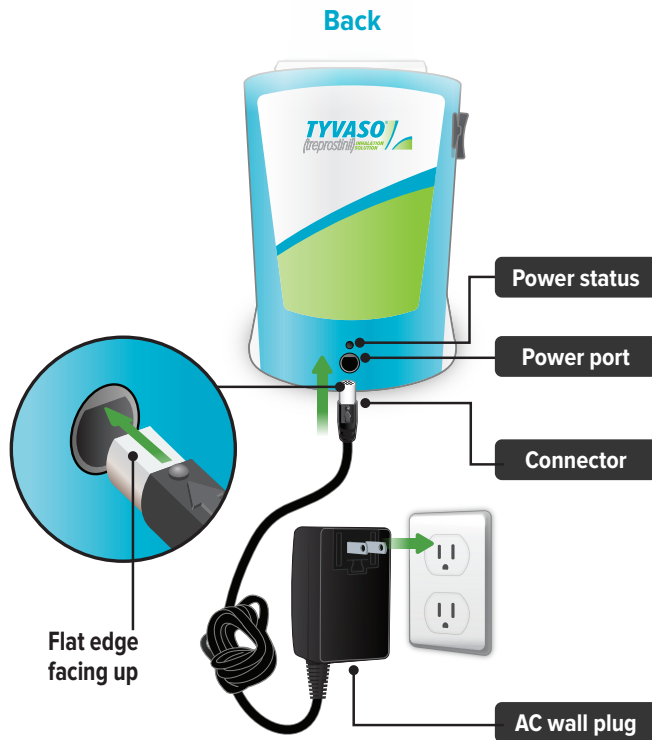
A: Charging device before use

1. Plug in device

Important: A new device might not be fully charged when you receive it. Always charge the device before you first use it. You can also charge the device overnight, when not in use and in between uses.

Plug the AC wall plug's white connector into the port on the back of the inhalation device. Then, plug the AC wall plug into the wall outlet.

The power status light above the port will light green when properly plugged in.



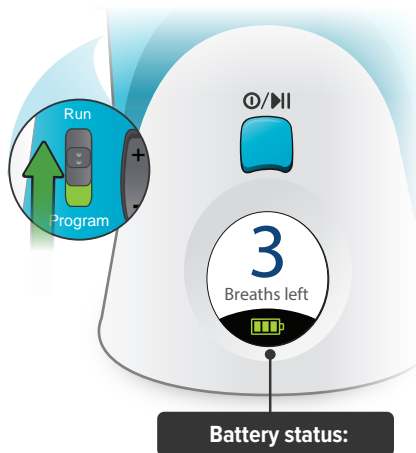
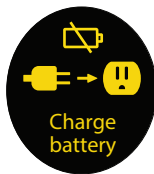
2. Check the battery's status

Make sure the Run / Program switch is set to Run. Press and **hold** the blue button to power on the device.

The battery icon at the bottom of the screen indicates battery status.

When you are done checking the battery status, press and **hold** the On/Off button until the display screen shuts off (note: letting the button go before the screen shuts off will start a treatment session).

If there is not enough charge to conduct a treatment session, "Charge battery" appears on screen.



Battery status:



Battery full



Battery more than half full



Battery less than half full



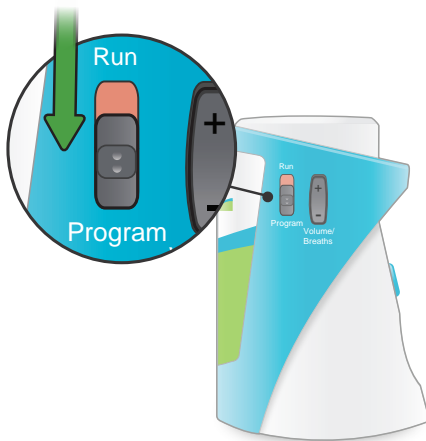
Battery almost empty

B: Setting your prescribed dose

Your doctor will prescribe the number of breaths you should take in each treatment session. You should program this number into the inhalation device before you use the device.

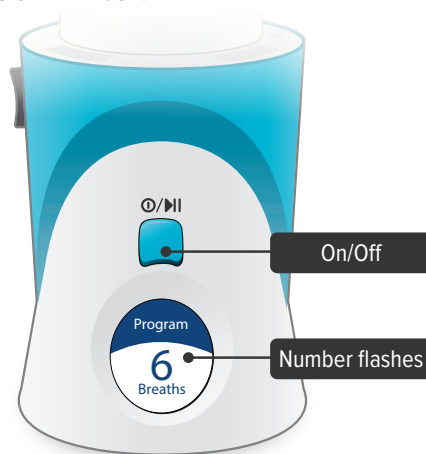
1. Switch to Program

Slide the Run / Program switch on the side of the device down to Program mode. In Program mode you enter the prescribed number of breaths for each dose. You cannot begin a treatment in Program mode.



2. Power on

Press and **hold** the On/Off button until the display screen turns on. The Program Breaths screen appears. The number of breaths currently set for each treatment session will flash.



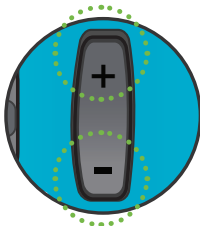
Program: Setting your prescribed dose

10049

3. Set breaths

Use the Volume / Breaths toggle button to enter your prescribed number of breaths onto the program screen.

increase breaths



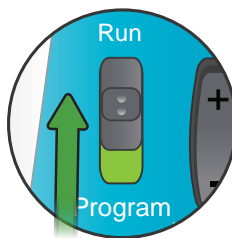
decrease breaths

Program mode



4. Switch to Run

Slide the Run / Program switch up to Run mode. Make sure your new breath count appears on screen.



Run mode



5. Power off

Press and **hold** the On/Off button until the display screen shuts off (note: letting the button go before the screen shuts off will start a treatment session).

Note: You will not need to program the breath count again, unless your prescribed number of breaths changes.



C: Adjusting device's audio volume

You can use the Volume / Breaths toggle button to adjust the volume of the audible signals (beeps) that the device provides as feedback during treatment sessions.

1. Switch to Run

Slide the Run / Program switch up to Run mode, if it is not in this position already.



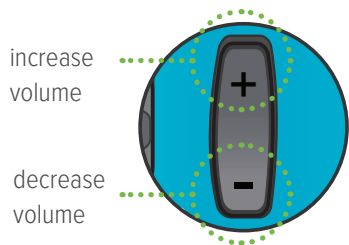
2. Power on

Press and **hold** the On/Off button until the display screen turns on, if it is not already turned on. The programmed number of breaths will appear with the words “Breaths left” and the battery icon at the bottom.



3. Adjust volume

With the Run / Program switch in the Run position, press then Volume / Breaths toggle button to access the Adjust Volume screen. Push **+** on the Volume / Breaths toggle button to increase beeping volume, or push **-** to decrease beeping volume.



audio off



mid-level
volume



maximum
volume

4. Power off

After adjusting the beeping volume up or down, the screen will display your new setting for a couple of seconds then return to the screen displaying the breaths left.

Press and **hold** the On/Off button until the display screen shuts off (note: letting the button go before the screen shuts off will start a treatment session).



Prepare
and use

Preparing and using your TYVASO Inhalation System for daily treatments

Section overview

This section provides instructions for preparing and using your TYVASO Inhalation System for daily treatments.

*Prepare
and use*

What you will need:

- ▶ A clean place to take your medicine
- ▶ TYVASO Inhalation device
- ▶ TYVASO Inhalation supplies
- ▶ One ampule of TYVASO Inhalation Solution

What is covered in this section:

A: Prepare a proper environment	28
B: Gather supplies	29
C: Fill water chamber and medicine cup	32
D: Assemble inhalation device	35
E: Power on inhalation device	40
F: Inhale your medicine	42

Important:

Before using the TYVASO Inhalation System, you should:

- Wash your hands.
- Make sure the device is resting on a stable, flat surface during assembly.



A: Prepare a proper environment

Follow these important instructions before setting up your treatment:

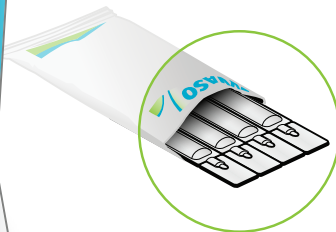
- Use the device in a quiet, distraction-free area.
- Try to use the device at times when your treatment will not be interrupted. If needed, you can pause your treatment (see page 44).
- Use the device in a comfortable space where you can stand or sit in an upright position.
- Use the device in an area where you can access a power source if you need to use the AC wall plug.
- The TYVASO Inhalation System is recommended for use indoors.
- Use the device in an area that provides enough space for the TYVASO Inhalation System and its accessories.
- Gather all necessary supplies on a stable, flat surface for assembly (see page 29 for list of supplies).
- Store the inhalation device at 15°C to 30°C (59°F to 86°F). Use at 15°C to 25°C (59°F to 77°F).
- Use the device in a well-lit area where you can clearly read these instructions, labels on the device, and the device screen.

B: Gather supplies

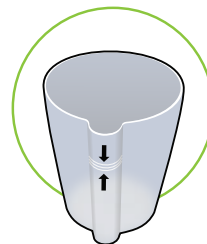
Gather the following supplies before starting treatment. Use only the supplies provided in the starter kit and monthly refill kit for correct device function. Prior to use, inspect each part and do not use parts if they appear damaged or dirty.



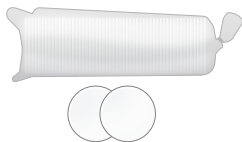
Inhalation device
Powered off



TYVASO ampules
Use 1 ampule per day

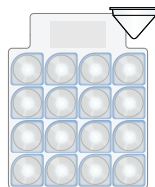


Water level cup
with 45 mL of distilled water



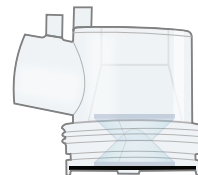
Filter membranes*

Use 2 per day

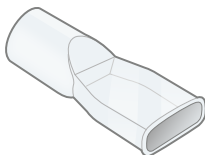


Medicine cups*

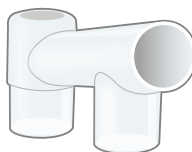
Use 1 per day



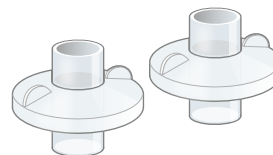
Dome assembly*



Mouthpiece*



Inhalation piece*



2 filter shells*

*These accessories are replaced every month. Replacement accessories are included in the Monthly Refill Kit.



2 Plugs*
(Used when storing the device)



Distilled water carrier



Carrying case



AC wall plug



Pen or pencil (not provided)
to record your treatment



Treatment Tracker Example

C: Fill water chamber and medicine cup

Important:

- **Wash your hands**



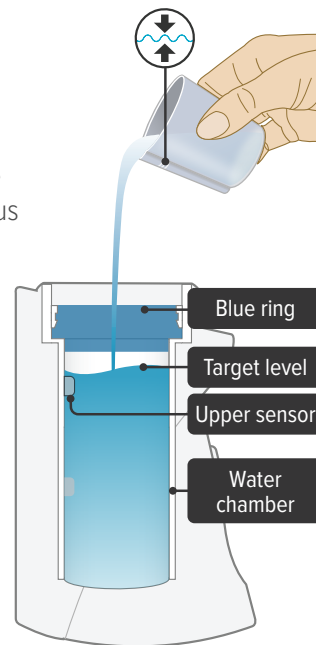
- **Unplug device** when filling to avoid damage to cords or connectors.
- **Only use distilled water** in the device. Distilled water is highly purified water that is required for the device to function properly. If you use another type of water (such as bottled or tap water), the device might not function properly. You can purchase distilled water at most grocery stores and pharmacies.

1. Fill water chamber

Fill the water level cup with distilled water up to the arrow markers on the water cup. Use fresh distilled water each day (i.e., do not use water left in the water chamber from the previous day). Pour the distilled water into the water chamber.

Make sure the water level is above the upper, silver sensor and below the blue ring in the water chamber (about 45 mL of distilled water).

Do not overfill the water chamber, or else the medicine cup might not fit correctly.

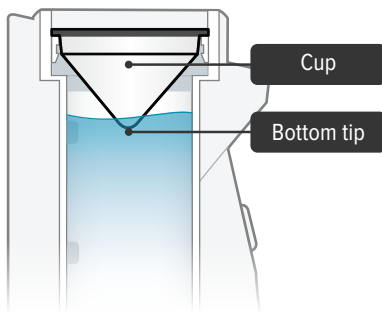


2. Place medicine cup

Obtain 1 new medicine cup and inspect it.

Do not use a medicine cup that is damaged (e.g., cracked or contains holes or dents), dirty, or was used before.

Place the empty medicine cup into the water chamber of the device, making sure that the cup's bottom tip is in the distilled water.



⚠ CAUTION: Make sure you place only 1 medicine cup. Placing multiple cups will prevent the flow of medicine.

3. Gather one ampule

Carefully cut open the top of the foil pouch, making sure not to cut the ampules. Each pouch contains 4 ampules. Remove 1 ampule of TYVASO.

Keep unused ampules in the foil pouch because the TYVASO medicine is sensitive to light. Write the date you first opened the pouch on the foil pouch.

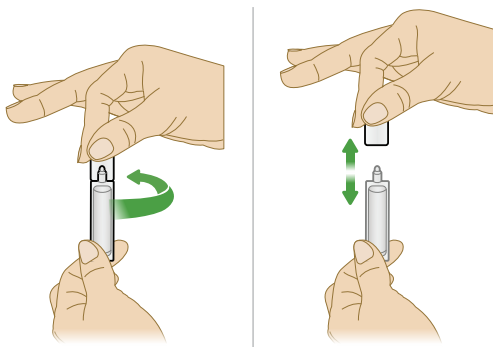
One ampule contains enough medicine for 1 day of treatment no matter how many breaths your doctor has prescribed.



⚠ CAUTION: Ampules must be used within 7 days of opening foil pouch. Open only 1 pouch at a time. Throw away (discard) any unused ampules after 7 days.

4. Open ampule

Gently hold the ampule in the upright (top up) position and twist off its top.

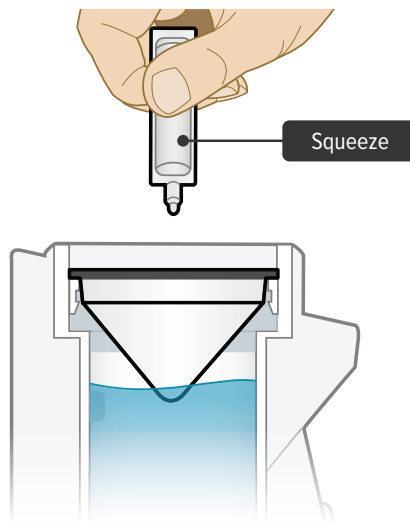


⚠ CAUTION: If any medicine from the ampule spills on your hands, wash your hands right away. Medicine contact with the skin can cause irritation.

5. Squeeze ampule

Point the ampule straight down toward the medicine cup's center to avoid spills.

Gently squeeze the medicine out of the ampule into the medicine cup. Squeeze until it is empty. Check to see that all of the medicine is in the medicine cup.



D: Assemble inhalation device

Important: Do not force parts together.

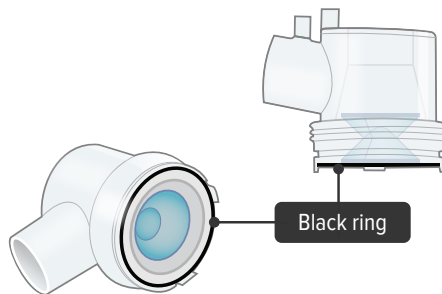
The TYVASO Inhalation System is designed so the parts only fit together properly one way. When the device is assembled correctly, the parts should fit together easily.



1. Check dome assembly

Visually check to make sure the black ring is securely placed in the dome assembly. The black ring should look like it does in the pictures below.

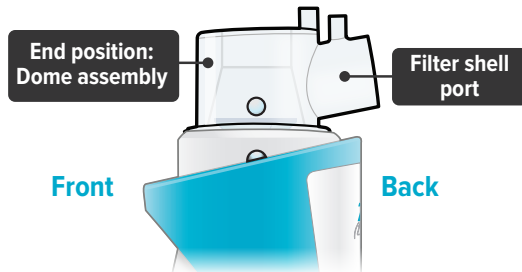
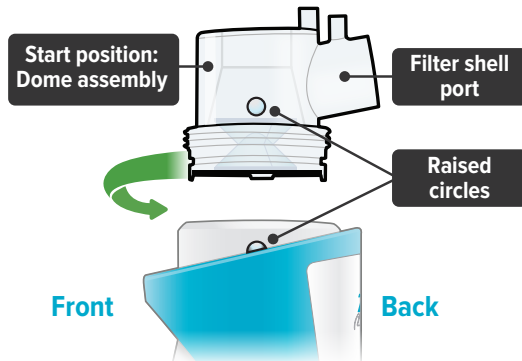
If the black ring is loose or missing, do not use the dome assembly. Throw it away and get a new one. If you need to order a new dome assembly, contact your specialty pharmacy provider.



2. Attach dome assembly

Align the raised circle on the side of the dome assembly with the raised circle on the side of the device.

Push down and screw the dome assembly onto the device clockwise (right) until the filter shell port is tight and pointed to the back of the device. You will hear clicks (or a slight crunching sound) as the dome assembly presses down on the medicine cup.



Important: The dome assembly “clicks” only the first time it connects to the medicine cup. If you then realign the dome assembly you will not hear another click.

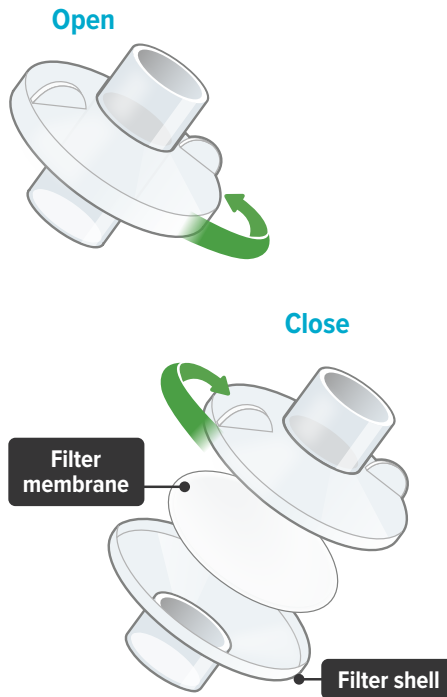
3. Install new filter membrane

Each day you will need to use a new filter membrane in each filter shell.

Note: New filter shells come with fresh filter membranes already installed.

To install a new filter membrane:

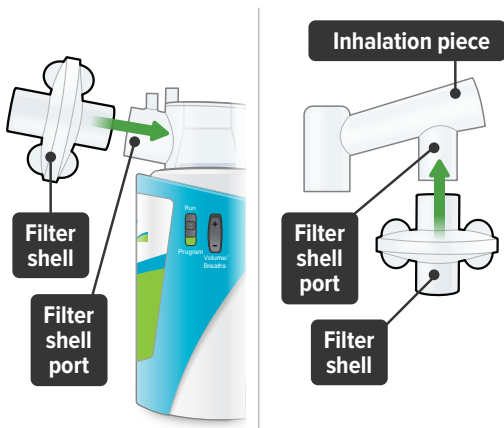
- ▶ a. Open the filter shell by unscrewing the 2 halves.
- ▶ b. Place a new filter membrane in 1 of the filter shell halves.
- ▶ c. Close the filter shell by screwing the 2 halves together until you can twist no further.
- ▶ d. Repeat steps a-c for second filter shell.



4. Attach filter shells

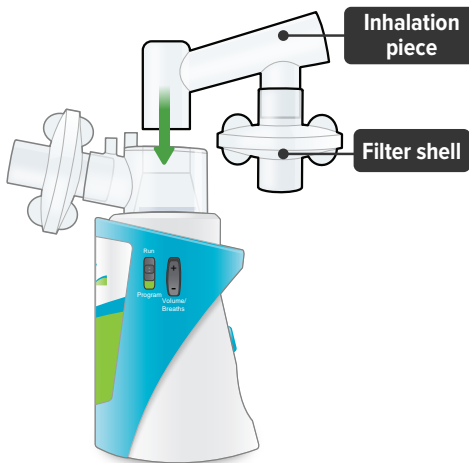
Insert 1 filter shell into the filter shell port on the side of the dome assembly and insert the second filter shell into the port on the bottom of the inhalation piece. The filter shells are the same and can be used in either port. You can turn the filter shells around to fit into the ports, as needed.

Make sure to insert filter shells straight into ports, not at an angle.



5. Insert inhalation piece

Insert the inhalation piece with attached filter shell into the upper opening of the dome assembly and turn it toward the front of the device. Gently push down the inhalation piece to make sure it is securely inserted in the dome assembly.



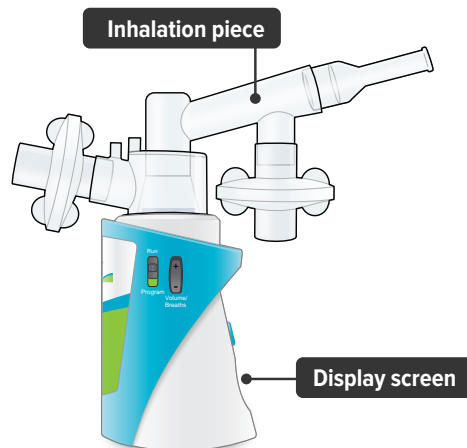
6. Insert mouthpiece

Carefully insert the mouthpiece into the inhalation piece.



7. Check assembled device

When the device is fully assembled, it should look like it does below. Slightly turn the inhalation piece so you can see the display screen, which provides important prompts during your treatment.



Important: Do not use device if you see liquid leaking from bottom of the device.

E: Power on inhalation device

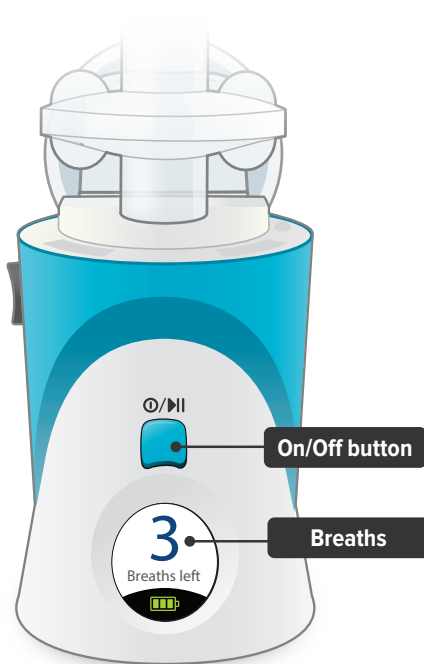
1. Power on device

Press and **hold** the On/Off button until the screen turns on and the device beeps once.

The screen will display the splash screen, then the time since your last treatment, then the current breaths programmed for each dose.

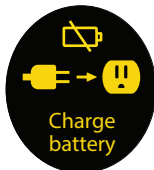


Important: Make sure the number on screen above "Breaths left" matches the prescribed number of breaths for that treatment session. If it does not match, see page 22 for instructions on setting the number of breaths for a treatment session.



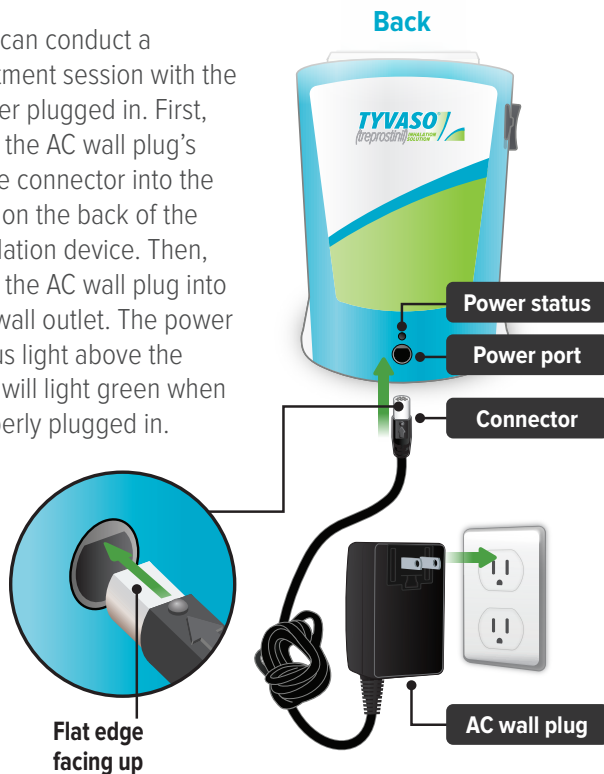
2. Plug in device, if needed

If the device's internal battery is too low to deliver a full treatment, the screen will display an instruction to plug in the power to charge the device battery. If the battery is fully depleted, the screen will not turn on.



You can charge the battery at any time, before the screen displays "Charge battery."

You can conduct a treatment session with the power plugged in. First, plug the AC wall plug's white connector into the port on the back of the inhalation device. Then, plug the AC wall plug into the wall outlet. The power status light above the port will light green when properly plugged in.



F: Inhale your medicine

1. Before starting, confirm treatment

You will breathe in (inhale) TYVASO during 4 treatment sessions each day (evenly spaced during your waking hours). During each treatment session, you will take a series of breaths through the mouthpiece of the TYVASO Inhalation System.

Before inhaling your medicine, ensure the Run/Program switch is in the 'Run' position, and make sure the number displayed on screen matches your prescribed number of breaths for that treatment session. During the treatment the device counts down each breath after a set time interval. Once you complete all breaths, record the breath number in your Treatment Tracker.

Important: If the number of breaths displayed does not match the number of breaths in your prescription, see page 22 “Setting your prescribed dose” and repeat steps 1-4.



Record number

Today, Monday, 11/23, I'm taking 3 breaths per treatment session.

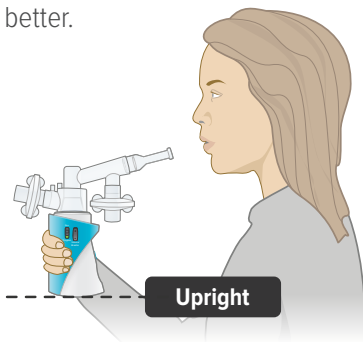
Time	8:15 AM	12:08 PM	4:00 PM	8:10 PM
Breaths completed	///	///	///	///
Questions and notes				

(Treatment Tracker example)

2. Hold the device upright

Hold the device upright and stand or sit in an upright position as shown below. Avoid covering the bottom of the device so that the audio speaker is not blocked.

Make sure you can see the display screen and lights clearly and that your hands do not cover the display screen or lights while holding device. If needed, you can move the inhalation piece and mouthpiece slightly to either side to see the screen and lights better.



See next page to start treatment.



Inhalation tips:

Technique:

When breathing each TYVASO treatment, be sure to keep the device level, directing the flow of medicine into the throat and not toward the roof of the mouth.

Seal your lips around the mouthpiece to ensure that you can inhale the full amount of TYVASO after it is produced by the device.

Inhalation:

Each breath should last approximately 3 seconds, breathing "normal full breaths." Do not hold your breath. Remove your lips from the mouthpiece, breathe out (exhale) normally and prepare for the next breath.

3. Press blue button to start treatment

If you need to pause treatment, you can press **and immediately** release (do not hold down) the blue button. Press the button again **and immediately** release to resume treatment. (Note: If you do not resume treatment after pausing, power off device.)



4. Wait

Look at the display screen for cues. Wait until you hear 2 short beeps. When you hear 1 long beep, exhale to prepare to inhale.



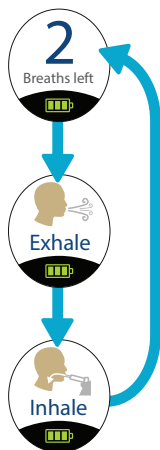
5. Inhale

When you hear 1 short beep and the indicator lights flash green, place your lips securely around the mouthpiece and inhale for 3 seconds. When lights stop flashing, remove lips from mouthpiece and exhale normally.



6. Repeat for each breath left

The screen will decrease the number of breaths left by 1. Repeat steps 4 and 5 for the number of prescribed breaths.



7. Finish session

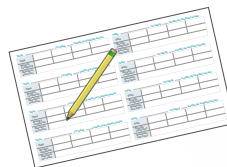
After displaying the last breath sequence, the green Done screen appears, you will hear a beep, and your treatment is done.



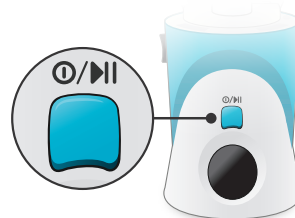
If the device is left in the "✓ Done" mode for more than 60 seconds, it will turn off automatically.

8. Record breaths, turn off device

Record the number of breaths you inhaled on the Treatment Tracker.



Press and **hold** blue button until screen turns off.



**Clean
and store**

⚠ CAUTION: If medicine does not appear to be flowing properly, the system might be set up incorrectly. See "Troubleshooting", starting on page 64 for details.

Cleaning and Storing your TYVASO Inhalation System

Section overview

This section provides instructions for storing your TYVASO Inhalation System after each treatment and daily and weekly cleaning.

There is also information about your monthly refill kits, replacing your device, and recharging the device's battery.

*Clean
and store*

What you will need:

- ▶ A clean place to work with the device
- ▶ TYVASO Inhalation device
- ▶ TYVASO Inhalation supplies

What is covered in this section:

A: Storing between sessions during the day	48
B: End of day cleaning	52
C: Recharging the battery	57
D: Weekly cleaning	59
E: Monthly Refill Kit	60
F: Replacing your devices	61

Important:

For further support, you can:

- Fill out and refer to your emergency contact information on the back of this Instructions for Use manual.
- Call 1-877-UNITHER (1-877-864-8437) for questions and information, or to report an adverse reaction.

A: Storing between sessions during the day

If you have more treatment sessions left in the day, perform the steps in this section.

If you have completed your last treatment session of the day, skip to “End of day cleaning” on page 52.

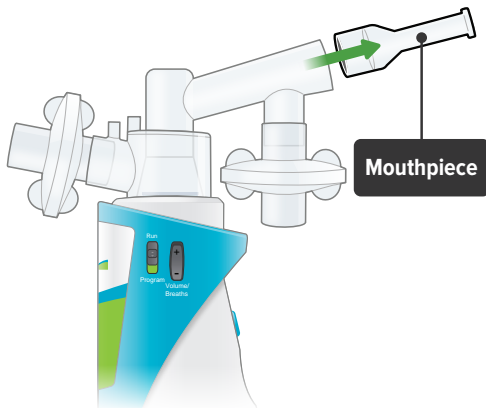
Be sure to pack all parts, including the AC wall plug, in the carrying case whenever transporting your device.

1. Disconnect AC wall plug

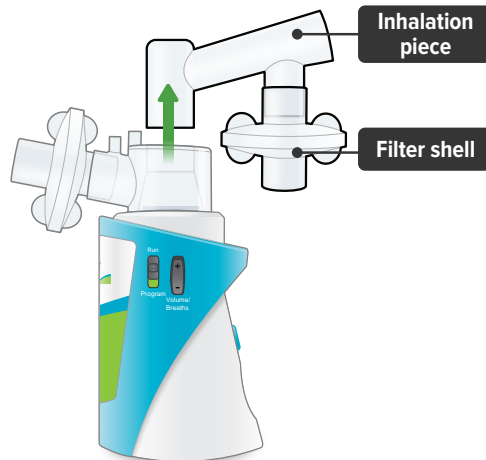
(if it is currently connected)



2. Remove mouthpiece



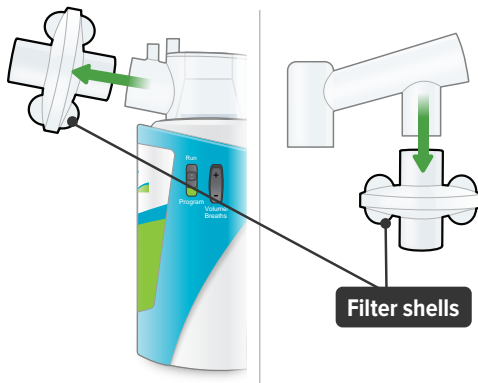
3. Remove inhalation piece



Important: When removing accessories between treatment sessions, hold the device by its base to avoid spilling the medicine.

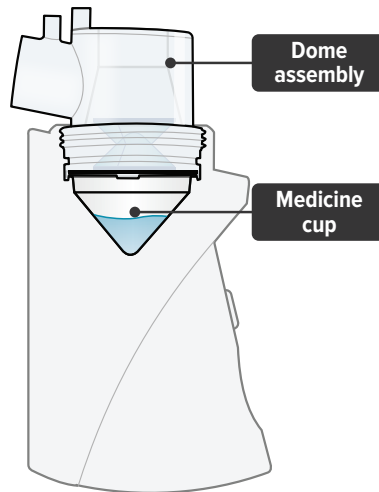
4. Remove both filter shells

Note: **Do not** remove the filter membranes from filter shells until after the last treatment session of the day.



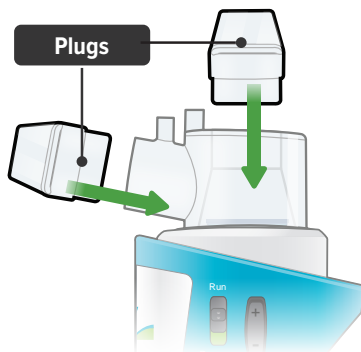
5. Leave dome assembly

Leave dome assembly and medicine cup (with the medicine still in it) attached to the device.



6. Place plugs in dome assembly

Insert a plug into each of the 2 open holes on the dome assembly to prevent the medicine from spilling out.

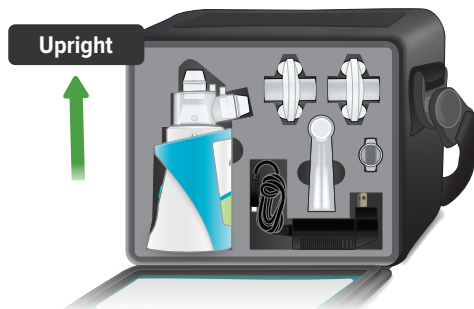


Important: If the plugs are not in place, the medicine may spill. If you spill any medicine, discard remaining medicine and start your next treatment with a new ampule.

7. Store in carrying case

You can store the inhalation device with the plugged dome assembly and disassembled accessories in the carrying case between treatment sessions.

Keep the carrying case upright while inserting the device and components so that water and medicine does not spill out of the device.



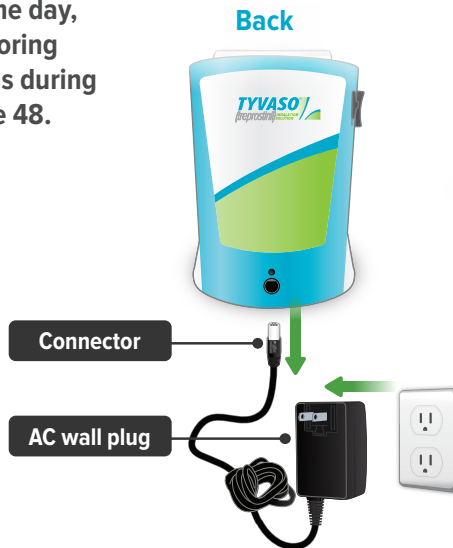
Important: Store the inhalation device in an upright position until the next treatment session. See “Specifications” on page 76 for additional storage and transport information.

B: End of day cleaning

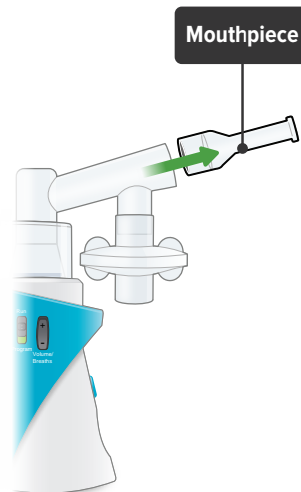
If you have completed your last treatment session of the day, perform the steps in this section.

If you have more treatment sessions left in the day, refer back to “Storing between sessions during the day” on page 48.

1. Disconnect AC wall plug
(if it is currently connected)



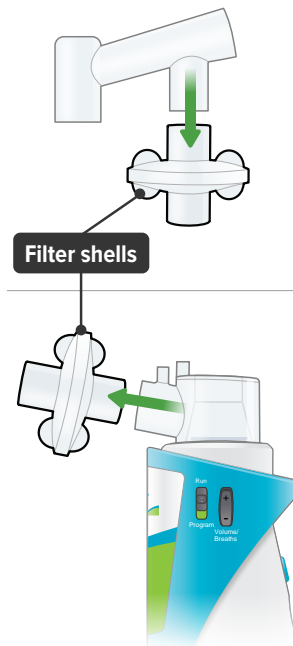
2. Remove mouthpiece



3. Remove inhalation piece with attached filter shell

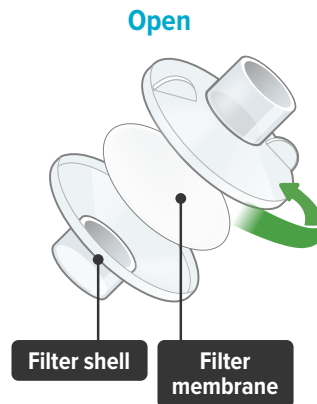


4. Remove both filter shells



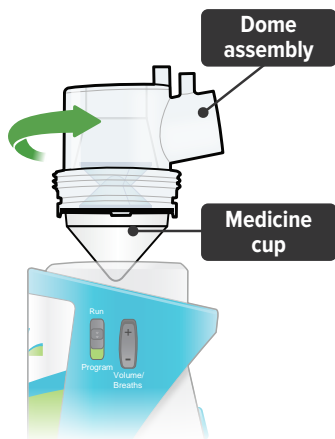
5. Discard filter membranes

Open filter shells by twisting in opposite directions. Remove and discard used filter membranes in the trash.



6. Remove dome assembly

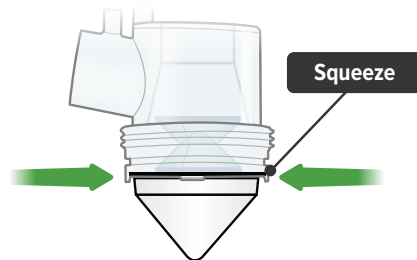
Remove the dome assembly by turning it counter-clockwise (to the left). The medicine cup should stay attached to the dome assembly.



7. Remove medicine cup

Remove the medicine cup by gently squeezing on the sides where it is attached to the dome assembly.

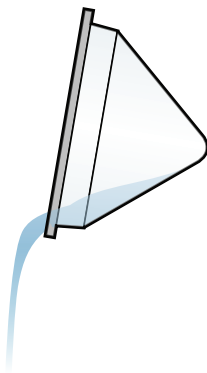
Be careful not to spill any leftover medicine.



⚠ CAUTION: If any medicine from the medicine cup spills on your hands, wash your hands immediately. Medicine contact with the skin can cause irritation.

8. Empty medicine cup

Empty any leftover medicine in the medicine cup into a waste basket, and discard the medicine cup.

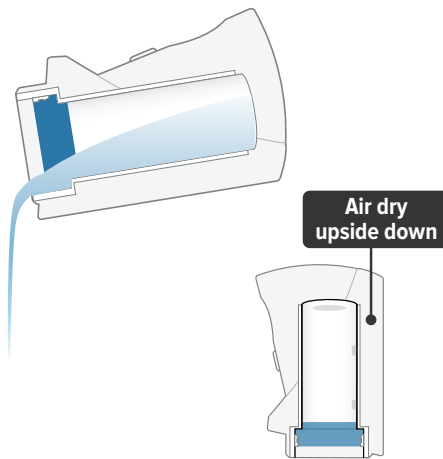


Important: Discard remaining TYVASO® (treprostinil) Inhalation Solution in an appropriate waste receptacle. Discard plastic medicine cup in the trash.

Do not reuse or recycle medicine cup.

9. Empty and clean device

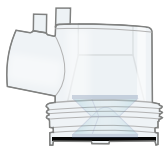
Empty distilled water from water chamber and let inhalation device air dry upside down. You can wipe the water chamber with a soft cloth or paper towel to remove any remaining water.



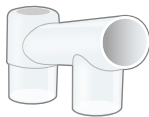
Important: Do not place the inhalation device in water or in a dishwasher.

10. Clean accessories

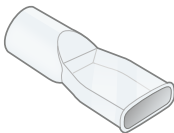
Clean accessories (pictured below) by hand in mild, soapy, warm water, then rinse them thoroughly with water. Allow accessories to air dry.



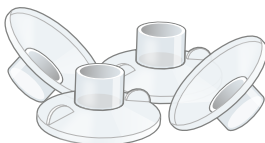
Dome assembly



Inhalation piece



Mouthpiece



Filter shells

Important: Do not place the inhalation device or its accessories in a microwave, conventional oven, or dishwasher.

11. Store components

Once all the items are dry, you can store the filter shells, inhalation piece, mouthpiece, dome assembly, AC wall plug, and inhalation device in the carrying case until the next day's treatment sessions.

You can also recharge the device for the next day of use (see page 57).

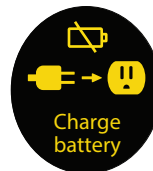


C: Recharging the battery

1. Checking the battery's status

You can recharge your battery at any time. Press and **hold** the blue button to power on the device to check battery status. Make sure the Run / Program switch is set to Run.

- The battery icon at the bottom of the screen indicates battery status:
- “Charge battery” appears on screen if there is not enough charge to conduct a treatment session.



Important: Always charge the device before you first use it. You should also charge the device when not in use and in between uses.

2. Charging the battery

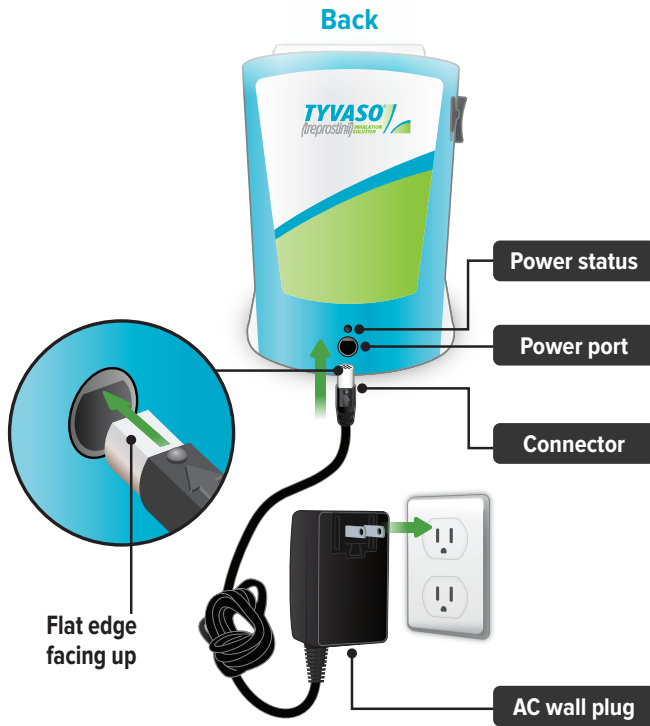
Plug the AC wall plug's white connector into the port on the back of the inhalation device. Then, plug the AC wall plug into the wall outlet. The power status light above the port will light green when properly plugged in.

The device battery might take up to 8 hours to fully charge.

If the device is powered on, the battery charging icon appears next to the battery icon at the bottom of the screen.



Battery charging icon

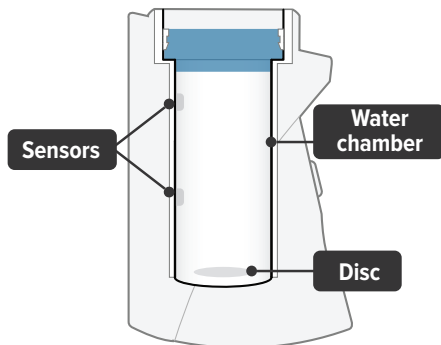


D: Weekly cleaning

Clean the device once a week to help avoid corrosion and leaks and to keep your device working properly.

Once a week, use a clean, dry cloth to wipe the interior of the water chamber. Make sure to wipe the 2 silver sensors and the white disc in the bottom of the water chamber.

You may wipe the exterior of the device with a damp cloth if the lights or buttons become difficult to see.



Interior



Exterior

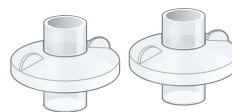
E: Monthly Refill Kit

Once a month, you will receive a refill kit that will come with a new set of accessories from your specialty pharmacy provider.

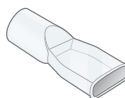
- Inspect the shipment to be sure all parts are included.
- Once the new kit has arrived, discard the used dome assembly, inhalation piece, mouthpiece, filter shells, and plugs.
- Do not recycle the used accessories.



Dome assembly



2 filter shells



Mouthpiece



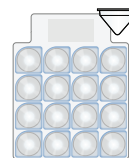
Inhalation piece



2 plugs



Filter membranes



Medicine cups

F: Replacing your devices

The inhalation devices should be replaced every 2 years from your first day of use. Replacement inhalation devices will be supplied by your specialty pharmacy provider.

When you receive a new inhalation device your specialty pharmacy provider will provide instructions for returning the old device.

*Help and
more info*

Help / More information about your TYVASO Inhalation System

Section overview

This section provides additional information about your device. Use this section to troubleshoot difficulties you have with the device, or to learn more about the device's specifications and warranty.

What you will need:

- ▶ Access to a phone (to contact support if troubleshooting steps do not resolve the problem)
- ▶ A clean place to work with the device
- ▶ TYVASO Inhalation Device or supplies, as needed

Help and
more info

What is covered in this section:

A: Troubleshooting	64
B: Specifications	76
C: Electromagnetic compatibility (EMC)	79
D: Glossary	87
E: Warranty information	90

Important:

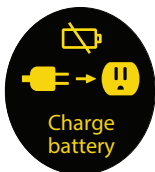
For further support, you can:

- Fill out and refer to your emergency contact information on the back of this Instructions for Use manual.
- Call 1-877-UNITHER (1-877-864-8437) for questions and information, or to report an adverse reaction.

A: Troubleshooting

Problem

**Charge Battery
screen appears**



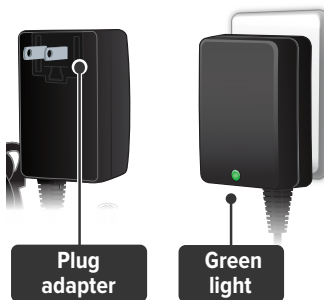
Possible causes

Low battery

Corrective actions

Charge the device battery by attaching the AC wall plug to an outlet. You can conduct a treatment session with the device plugged in.

AC wall plug not properly connected



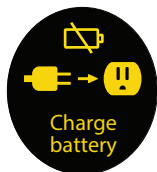
Ensure that the plug adapter piece (the detachable piece with the metal prongs) is securely attached to the AC wall plug. Then, make sure the AC wall plug is properly connected to an outlet and device. The status lights on the back of the AC wall plug and device should light green. You can conduct a treatment session with the device plugged in.

“Charge battery screen” troubleshooting continues on next page.



Problem

**Charge Battery
screen appears
(continued)**

**Possible causes**

AC wall plug is defective

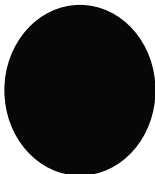
**Corrective actions**

Use the replacement AC wall plug. Confirm that status light on AC wall plug is green when plugged in. You can conduct a treatment session with the device plugged in.

If device still does not function after taking corrective actions listed above, contact your specialty pharmacy provider for assistance.

Problem

Screen does not turn on



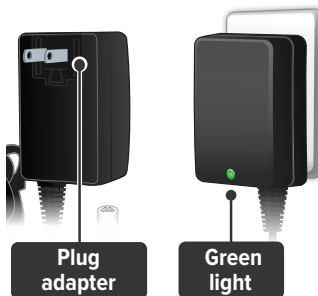
Possible causes

Device battery is completely empty

Corrective actions

Charge the device battery by attaching the AC wall plug to an outlet. You can conduct a treatment session with the device plugged in.

AC wall plug not properly connected



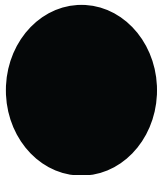
Ensure that the plug adapter piece (the detachable piece with the metal prongs) is securely attached to the AC wall plug. Then, make sure the AC wall plug is properly connected to an outlet and device. The status lights on the back of the AC wall plug and device should light green. You can conduct a treatment session with the device plugged in.

“Screen does not turn on” troubleshooting continues on next page.



Problem

**Screen does not
turn on (continued)**

**Possible causes**

AC wall plug is defective

**Corrective actions**

Use the replacement AC wall plug. Confirm that status light on AC wall plug is green when plugged in. You can conduct a treatment session with the device plugged in.

If device still does not function after taking corrective actions listed above, contact your specialty pharmacy provider for assistance.

**Call Support screen
appears**



Temporary device failure.

Unplug device, if plugged in, and power off device. Power on device and check that Call Support screen does not reappear. Continue treatment.

If device still does not function after taking corrective actions listed above, contact your specialty pharmacy provider for assistance.

Problem

Loss of power during treatment

Possible causes

Device is disconnected from power source and battery is empty

Corrective actions

Reconnect device to power source and confirm the power status light on back of device is green (battery is charging). Press and **hold** the blue On/ Off button to turn on the device. The display will show how many breaths are left in that treatment session. Press **and immediately** release (do not hold down) the blue button again to continue your treatment session.

Power source is temporarily disrupted (for example, electricity interruption due to a storm)

Reconnect device to power source and confirm the power status light on back of device is green (battery is charging). Press and **hold** the blue On/ Off button to turn on the device. The display will show how many breaths are left in that treatment session. Press **and immediately** release (do not hold down) the blue button again to continue your treatment session.

If device still does not function after taking corrective actions listed above, contact your specialty pharmacy provider for assistance.

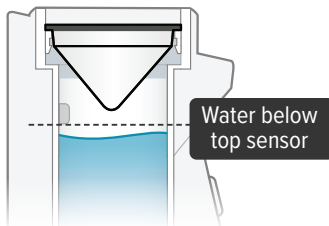
Problem

Add Water screen appears



Possible causes

Water chamber is empty or distilled water level is too low.



Corrective actions

Unplug device, if plugged in, and power off device. Remove dome assembly (making sure not to spill medicine) and place it aside, keeping it upright. Then empty water chamber.

Refill water chamber with distilled water using water level cup (see page 32). Reassemble device. Power the device on and continue treatment.

“Add water screen” troubleshooting continues on next page.



Problem

**Add Water screen
appears (continued)**



Possible causes

The distilled water is too pure.

Corrective actions

Unplug device, if plugged in, and power off device. Remove dome assembly (making sure not to spill medicine) and place it aside, keeping it upright. Then empty water chamber.

Add 1 teaspoon of tap water to the water level cup. Fill rest of cup with distilled water up to level between the 2 arrow markings on cup (see page 32). Pour cup's contents into water chamber. Reassemble device. Power the device on and continue treatment.

"Add water screen" troubleshooting continues on next page.

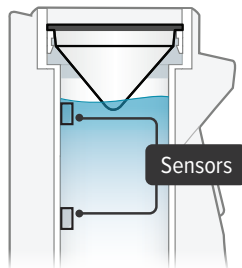


Problem

**Add Water screen
appears (continued)**

**Possible causes**

Water level sensors have a thin layer of build-up

**Corrective actions**

Unplug device, if plugged in, and power off device. Remove dome assembly (making sure not to spill medicine) and place it aside, keeping it upright. Then empty water chamber.

Clean sensors and interior surfaces of water chamber with a clean cloth. Refill water chamber with distilled water using water level cup (see page 32). Reassemble device. Power the device on and continue treatment.

If device still does not function after taking corrective actions listed above, contact your specialty pharmacy provider for assistance.

Problem

No “click” (or crunch) was heard when attaching the dome assembly

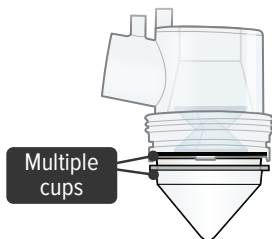
Possible causes

No medicine cup in the water chamber of the device

Corrective actions

Unplug device, if plugged in, and power off device. Place an empty medicine cup into the water chamber of the device and fill it with 1 ampule of TYVASO. Reassemble device. Power the device on and continue treatment.

Multiple medicine cups attached to the dome assembly



Unplug device, if plugged in, and power off device. Remove and dispose of all medicine cups in the device. Place a single, new medicine cup into device water chamber and fill with 1 ampule of TYVASO. Reassemble device. Power the device on and continue treatment.

“No “click” (or crunch)” troubleshooting continues on next page.



Problem

No “click” (or crunch) was heard when attaching the dome assembly (continued)

Possible causes

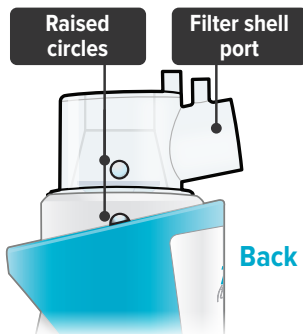
Dome assembly is not securely in place

Corrective actions

Unplug device, if plugged in, and power off device.

Align the raised circle on the side of the dome assembly with the raised circle on the side of the device.

Push down and screw the dome assembly onto the device clockwise (right) until the filter shell port is tight and pointed to the back of the device and the raised circles line up again. You will hear clicks (or crunch sound) as the dome assembly presses down on the medicine cup. Reassemble device. Power the device on and continue treatment.



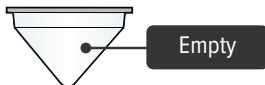
If device still does not function after taking corrective actions listed above, contact your specialty pharmacy provider for assistance.

Problem

No medicine comes out of the device during a treatment session

Possible causes

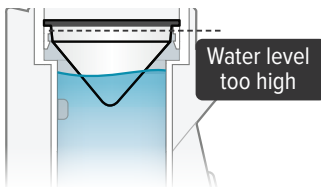
No TYVASO® (treprostinil) Inhalation Solution in the medicine cup



Damaged medicine cup



Distilled water level in the water chamber is too high

**Corrective actions**

Unplug device, if plugged in, and power off device. Fill medicine cup with 1 ampule of TYVASO. Reassemble device. Power the device on and continue treatment.

Unplug device, if plugged in, and power off device. Remove and dispose of the medicine cup in the device. Empty the water chamber then refill it with 45 mL of distilled water (see page 32). Place a single, new medicine cup into water chamber and fill with 1 ampule of TYVASO. Reassemble device. Power the device on and continue treatment.

Unplug device, if plugged in, and power off device. Remove dome assembly (making sure not to spill medicine) and place it aside, keeping it upright. Empty the water chamber then refill it with 45 mL of distilled water (see page 32). Reassemble device. Power the device on and continue treatment.

"No medicine comes out" troubleshooting continues on next page.

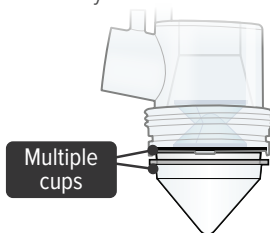


Problem

No medicine comes out of the device during a treatment session (continued)

Possible causes

Multiple medicine cups attached to the dome assembly

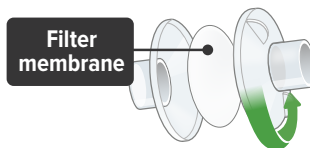
**Corrective actions**

Unplug device, if plugged in, and power off device. Remove and dispose of all medicine cups in the device. Place a single, new medicine cup into water chamber and fill with 1 ampule of TYVASO. Reassemble device. Power the device on and continue treatment.

If device still does not function after taking corrective actions listed above, contact your specialty pharmacy provider for assistance.

Difficult to breathe in medicine through the mouthpiece

Filter membrane is clogged



Unplug device, if plugged in, and power off device. Replace both filter membranes (see page 37). Reassemble device. Power the device on and continue treatment.

If device still does not function after taking corrective actions listed above, contact your specialty pharmacy provider for assistance.

B: Specifications

Inhalation Device

Model	TD-300/A
Size	3.5" x 3.2" x 4.7" (90 x 82 x 120 mm)
Weight, inhalation device	365 g (12.8 oz)
Types of power supply	AC wall plug, 120 V, 60 Hz
Power input	14 V DC, 1.1 A maximum
Operating power consumption	18 Watt maximum
Ultrasonic frequency	2.4 MHz (nominal)
Nebulization rate	0.50 - 0.55 mg/min (0.9% Saline)
Medicine cup capacity	6 mL, nominal
Water chamber capacity	45 mL, nominal
Electric protection class	II, Type BF
Storage temperature/humidity	15 to 30°C/20-80% relative humidity
Operating temperature/humidity	15 to 25°C/40-75% relative humidity
A-weighted sound pressure level	75 dBA (1 m), maximum

Packaging Dimensions (Approximate Length x Width x Height)

Patient Starter Kit (PSK)	12.2" x 14.3" x 16.0"
Monthly Refill Kit (MRK)	9.9" x 6.1" x 16.1"
Institutional Starter Kit (ISK)	12.2" x 14.3" x 16.0"

TYVASO Mass and Particle Specifications for 9 breaths

Mass Median Aerodynamic Diameter (MMAD)*	mean = 2.0 μ m SD = 0.3
Total Emitted Dose per Breath**	mean = 6.0 μ g SD = 0.4
Total Aerosol Mass*	mean = 58 μ g SD = 5.9
Total Respirable Dose*	mean = 44.6 μ g SD = 3.5
Respirable Fraction*	mean = 73% SD = 5
Geometric Standard Deviation (GSD)*	mean = 2.6 SD = 0.4

*n=108 data points from r=3 inhalation devices. Each data point was 9 breaths.

**n=216 data points from r=6 inhalation devices. Each data point was 1 breath.

Accessories

TD-300N-US	AC wall plug
ON-102/1/C	Medicine cup, Quantity-16
ON-109	Filter membranes
ON-120/C	Plugs
ON-101/C	Filter shell
TD-103/C	Dome assembly with baffle plate
ON-104/C	Inhalation piece
ON-105/C	Mouthpiece
TD-118	Water level cup
TD-158	Carrying case
TD-155	Distilled water carrier

Note: Part number subject to change.

C: Electromagnetic compatibility (EMC)

The TYVASO Inhalation System has been tested and found to comply with the electromagnetic compatibility (EMC) limits for medical devices according to IEC 60601-1-2: (2007). Compliance is intended to provide reasonable protection against harmful interference in a typical user environment.

Table 1, Table 2 and Table 3 document the intended EMC use environment and established compliance levels for the TYVASO Inhalation System. To ensure the intended performance, use the system in the environments described in these tables.

The TYVASO Inhalation System is intended for use in the electromagnetic environment specified in this section.

Table 1: Guidance and manufacturer's declaration - electromagnetic emissions

Guidance and manufacturer's declaration - electromagnetic emissions		
The TYVASO Inhalation System is intended for use in the electromagnetic environment specified below. The customer or the user of the TYVASO Inhalation System should assure that it is used in such an environment.		
Emissions test	Compliance	Electromagnetic environment - guidance
RF emissions CISPR 11	Group 1	The TYVASO Inhalation System uses RF energy only for its internal function. Therefore, its RF emissions are very low and are not likely to cause any interference in nearby electronic equipment.

Table 1: Guidance and manufacturer's declaration - electromagnetic emissions (continued)

Guidance and manufacturer's declaration - electromagnetic emissions (continued)		
Emissions test	Compliance	Electromagnetic environment - guidance
RF emissions CISPR 11	Class B	The TYVASO Inhalation System is suitable for use in all establishments, including domestic establishments and those directly connected to the public low voltage power supply network that supplies buildings used for domestic purposes.
Harmonic emissions IEC 61000-3-2	Class A	
Voltage fluctuations/ flicker emissions IEC 61000-3-3	Complies	

Table 2: Guidance and manufacturer's declaration – electromagnetic immunity

Guidance and manufacturer's declaration – electromagnetic immunity			
The TYVASO Inhalation System is intended for use in the electromagnetic environment specified below. The customer or the user of the TYVASO Inhalation System should assure that it is used in such an environment.			
Immunity test	IEC 60601 Test level	Compliance level	Electromagnetic environment - guidance
Electrostatic discharge (ESD) IEC 61000-4-2	± 8 kV contact ± 15 kV air	± 8 kV contact ± 15 kV air	Floors should be wood, concrete or ceramic tile. If floors are covered with synthetic material, the relative humidity should be at least 30%.
Electrical fast transient/burst IEC 61000-4-4	± 2 kV for power supply lines ± 1 kV for input/output lines	± 2 kV for power supply lines ± 1 kV for input/output lines	Mains power quality should be that of a typical commercial or hospital environment.
Surge IEC 61000-4-5	± 1 kV line(s) to line(s) ± 2 kV line(s) to earth	± 1 kV line(s) to line(s) ± 2 kV line(s) to earth	Mains power quality should be that of a typical commercial or hospital environment.

Table 2: Guidance and manufacturer's declaration – electromagnetic immunity (continued)

Guidance and manufacturer's declaration – electromagnetic immunity (continued)			
Immunity test	IEC 60601 Test level	Compliance level	Electromagnetic environment - guidance
Voltage dips, short interruptions and voltage variations on power supply input lines IEC 61000-4-11	$0\% U_T$ (100 % dip in U_T) for 0,5 cycle $0\% U_T$ (100 % dip in U_T) for 1 cycle $70\% U_T$ (30 % dip in U_T) for 25/30 cycles $0\% U_T$ (100 % dip in U_T) for 250/300 cycle	$0\% U_T$ (100 % dip in U_T) for 0,5 cycle $0\% U_T$ (100 % dip in U_T) for 1 cycle $70\% U_T$ (30 % dip in U_T) for 25/30 cycles $0\% U_T$ (100 % dip in U_T) for 250/300 cycle	Mains power quality should be that of a typical commercial or hospital environment. If the user of the TYVASO Inhalation System requires continued operation during power mains interruptions, it is recommended that the TYVASO Inhalation System be powered from an uninterruptible power supply or the internal battery.
Power frequency (50/60 Hz) magnetic field IEC 61000-4-8	30 A/m	30 A/m	Power frequency magnetic fields should be at levels characteristic of a typical location in a typical commercial or hospital environment.
NOTE U_T is the a.c. mains voltage prior to application of the test level.			

Table 2: Guidance and manufacturer's declaration – electromagnetic immunity (continued)

Guidance and manufacturer's declaration – electromagnetic immunity (continued)			
Immunity test	IEC 60601 Test level	Compliance level	Electromagnetic environment - guidance
Conducted RF IEC 61000-4-6	3 Vrms 150 kHz to 80 MHz	3 Vrms 150 kHz to 80 MHz	<p>Portable and mobile RF communications equipment should be used no closer to any part of TYVASO Inhalation System, including cables, than the recommended separation distance calculated from the equation applicable to the frequency of the transmitter.</p> <p>Recommended separation distance</p> $d = 1.2 \sqrt{P}$ $d = 1.2 \sqrt{P} \text{ 80 MHz to 800 MHz}$ $d = 2.3 \sqrt{P} \text{ 800 MHz to 2.5 GHz}$ <p>where P is the maximum output power rating of the transmitter in watts (W) according to the transmitter manufacturer and d is the recommended separation distance in meters (m).</p> <p>Field strengths from fixed RF transmitters, as determined by an electromagnetic site survey^a, should be less than the compliance level in each frequency range^b.</p> <p>Interference may occur in the vicinity of equipment marked with the following symbol:</p>
Radiated RF IEC 61000-4-3	10 V/m 80 MHz to 2.6 GHz	10 V/m 80 MHz to 2.6 GHz	



Table 2: Guidance and manufacturer's declaration – electromagnetic immunity (continued)

Guidance and manufacturer's declaration – electromagnetic immunity (continued)
NOTE 1: At 80 MHz and 800 MHz, the higher frequency range applies.
NOTE 2: These guidelines may not apply in all situations. Electromagnetic propagation is affected by absorption and reflection from structures, objects and people.
^a Field strengths from fixed transmitters, such as base stations for radio (cellular/cordless) telephones and land mobile radios, amateur radio, AM and FM radio broadcast and TV broadcast cannot be predicted theoretically with accuracy. To assess the electromagnetic environment due to fixed RF transmitters, an electromagnetic site survey should be considered. If the measured field strength in the location in which the TYVASO Inhalation System is used exceeds the applicable RF compliance level above, the TYVASO Inhalation System should be observed to verify normal operation. If abnormal performance is observed, additional measures may be necessary, such as re-orienting or relocating the TYVASO Inhalation System.
^b Over the frequency range 150 kHz to 80 MHz, field strengths should be less than [V1] V/m.

Table 3: Manufacturer's Declaration – Recommended separation distances between portable and mobile communications equipment and the TYVASO Inhalation System

Recommended separation distances between portable and mobile RF communications equipment and the TYVASO Inhalation System			
The TYVASO Inhalation System is intended for use in an electromagnetic environment in which radiated RF disturbances are controlled. The customer or the user of the TYVASO Inhalation System can help prevent electromagnetic interference by maintaining a minimum distance between portable and mobile RF communications equipment (transmitters) and the TYVASO Inhalation System as recommended below, according to the maximum output power of the communications equipment.			
Rated maximum output power of transmitter W	Separation distance according to frequency of transmitter m		
	150 kHz to 80 MHz $d = 1.2 \sqrt{P}$	80 MHz to 800 MHz $d = 1.2 \sqrt{P}$	800 MHz to 2.5 GHz $d = 2.3 \sqrt{P}$
0.01	0.12	0.12	0.23
0.1	0.38	0.38	0.73
1	1.2	1.2	2.3
10	3.8	3.8	7.3
100	12	12	23

Table 3: Manufacturer's Declaration – Recommended separation distances between portable and mobile communications equipment and the TYVASO Inhalation System (continued)

Recommended separation distances between portable and mobile RF communications equipment and the TYVASO Inhalation System (continued)

For transmitters rated at a maximum output power not listed above, the recommended separation distance d in meters (m) can be estimated using the equation applicable to the frequency of the transmitter, where P is the maximum output power rating of the transmitter in watts (W) according to the transmitter manufacturer.

NOTE 1: At 80 MHz and 800 MHz, the separation distance for the higher frequency range applies.

NOTE 2: These guidelines may not apply in all situations. Electromagnetic propagation is affected by absorption and reflection from structures, objects and people.

D: Glossary

Accessories: Parts of the TYVASO Inhalation System. See page 29.

Ampule: A sealed, lightweight clear plastic vial containing a 1-day supply of TYVASO® (treprostinil) Inhalation Solution.

Black ring: A round seal that fits on the bottom of the dome assembly. The seal helps ensure that TYVASO does not mix with the distilled water in the water chamber.

Display screen: A small area on the inhalation device that provides instructions and device information.

Distilled water: Water that is highly purified so that it contains only essential elements.

Dome assembly: The plastic accessory that contains the baffle plate and connects the mouthpiece, inhalation piece, and filter shells to the base of the inhalation device.

Filter membrane: The white pad that goes into the filter shells.

Filter shells: Plastic accessories that hold the filter membranes.

Inhalation indicator lights: Two green lights on the top surface of the inhalation device that signals when you should inhale.

Inhalation piece: The plastic accessory that connects the mouthpiece with the dome assembly.

Inhalation device: The base of the TYVASO Inhalation System to which the accessories connect. The inhalation device contains the display screen and lights.

Inhale: How you will breathe in TYVASO with the TYVASO Inhalation System.

Medicine cup: The disposable plastic cone-shaped cup into which TYVASO is poured. The medicine cup fits inside the water chamber.

Mouthpiece: The plastic part that you will breathe through (using your mouth) to inhale TYVASO.

On/Off, Start/Pause (blue) button: A manually activated control on the front of the device that switches between fully on and fully off power states. Once the device power is on, the button begins or pauses treatment.

Plugs: Plastic accessories that are inserted into the openings of the dome assembly between treatment sessions. Plugs help keep TYVASO from spilling if the inhalation device tips over.

Power status light: LED on the back of the device that lights green when power is connected and battery is charging.

Power port: Port on back of device for plugging into a power source using the AC wall plug.

Prompts: The audio and visual signals that help guide you through the treatment sessions.

Run / Program switch: A manually activated control on the side of the device that switches between the modes for delivering treatment (Run) and programming breaths (Program).

Sensors: The silver objects on the inside wall of the water chamber. The sensors must be covered with distilled water for the TYVASO Inhalation System to function properly.

Specialty pharmacy provider: A pharmacy that carries only specialized medicines and medical devices. Your specialty pharmacy provider is a good source of information about TYVASO and the TYVASO Inhalation System.

Treatment session: 1 of 4 daily sessions during which you will take TYVASO with a specific number of inhalations.

TYVASO: The prescription medicine that you will use with the TYVASO Inhalation System.

Volume / Breaths toggle button: A manually activated control on the side of the device that increases or decreases audio volume (when in Run mode) and programmed breaths (when in Program mode).

Water chamber: The white hollow portion in the center of the inhalation device into which distilled water and the medicine cup are placed.

E: Warranty information

Your TYVASO Inhalation System is granted a replacement or repair warranty good for 2 years from your date of receipt of the TYVASO Inhalation System or 5 years from the date of manufacture, whichever comes first. This warranty applies to the TYVASO Inhalation System device only. Accessory components are not covered under warranty.

Circumstances that may void your warranty include:

- ▶ Modification or disassembly of the TYVASO Inhalation System device by anyone other than a factory-authorized technician
- ▶ Failure to comply with this written Instructions for Use manual when operating the TYVASO Inhalation System
- ▶ Unapproved use of the TYVASO Inhalation System

For all inquiries relating to service or warranty for your TYVASO Inhalation System, contact your specialty pharmacy provider.

You should have the following information available:

- ▶ Device serial number (located on bottom of TYVASO Inhalation System)

- ▶ Date TYVASO Inhalation System was acquired

- ▶ Nature of the problem and any steps taken to fix it

Overview

TYVASO®
INHALATION SYSTEM

#: 10118

TYVASO®
(treprostinil) INHALATION
SOLUTION

Program
before use

TYVASO Inhalation Solution is for prescription use only.

Emergency contact information

► Clinician:

► Nurse educator:

► Specialty pharmacist:

► United Therapeutics:

Prepare
and use

Clean
and store

Help and
more info

For further questions and information, or to report a problem with your device or an adverse event with your TYVASO Inhalation System, please call 1-877-UNITHER (1-877-864-8437).



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United Therapeutics Corporation
Research Triangle Park, North Carolina 27709

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United Therapeutics Corporation.

This Instructions for Use has been
approved by the U.S. Food and Drug
Administration.

Revised: August 2022

LIQ_PH-ILD_00002638

EXHIBIT 19

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS CORPORATION,)

Plaintiff,) C.A. No. 23-975 (RGA)

v.)

LIQUIDIA TECHNOLOGIES, INC.,)

Washington, D.C.

Sunday, March 10, 2024

Deposition of STEVEN D. NATHAN, M.D., a
witness herein, called for examination by counsel
for the Defendant in the above-entitled matter,
pursuant to notice, the witness being duly sworn by
Barbara J. Moore, a Notary Public in and for the
District of Columbia, taken at the offices of
GOODWIN PROCTOR, LLP, 1900 N Street, NW,
Washington, D.C., at 9:00 a.m., and the proceedings
being taken down by Stenotype by BARBARA MOORE,
CRR, RMR, and transcribed under her direction.



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PROCEEDINGS

THE VIDEOGRAPHER: We are now on the record. This begins videotape Number 1 in the deposition of Dr. Steven Nathan in the matter of United Therapeutics Corporation v. Liquidia Technology in the District Court of Delaware, Case No. 23-975.

Today is March 10, 2024. The time is 9:01. This deposition is being taken at 1900 N Street, NW, Washington, D.C., at the request of Cooley, LLC.

The videographer is Bradley Loy of Magna Legal Services, and the court reporter is Barbara Moore, Magna Legal Services.

Would counsel please state their appearances and who they represent.

ATTORNEY DAVIES: Jonathan Davies from Cooley for the defendant Liquidia, and with me today are my colleagues, Brittney Cazakoff and Sanya Sukduang.

ATTORNEY DYKHUIS: Art Dykhuis with McDermott Will & Emery for the plaintiff and the witness, Liquidia

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Page 7

1 Therapeutics. Also with me is Gabriel
2 Ferrante.
3 *****
4 STEVEN D. NATHAN, M.D.,
5 having been called as a witness on behalf of the
6 Plaintiff and having been first duly sworn, was
7 examined and testified as follows:
8 EXAMINATION BY
9 ATTORNEY DAVIES:
10 Q. Okay. Good morning, Dr. Nathan.
11 How are you?
12 A. I'm good. How are you doing?
13 Q. Could you state your address for the
14 record.
15 A. [REDACTED]
16 [REDACTED].
17 Q. Have you been deposed before?
18 A. Yes, I have.
19 Q. About how many times?
20 A. It's in my declaration, but I
21 believe it's three or four times.
22 Q. So today you understand you're under
23 oath, and it's the same oath that you would be
24 under if you were testifying in court; correct?
25 A. Yes.

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1 A. None.
2 Q. When was the first time that you
3 were contacted by counsel for United Therapeutics
4 about assisting in this matter?
5 A. It was sometime at the beginning of
6 February.
7 Q. February of this year?
8 A. 2024, yes.
9 Q. And who contacted you?
10 A. I think it was a gentleman by the
11 name of Adam Horowitz.
12 Q. When did you begin working on the
13 declaration that you submitted in this case?
14 A. It was also sometime around the
15 beginning of February.
16 Q. First week of February, do you
17 think?
18 A. Approximately.
19 Q. And in preparing your declaration,
20 what attorneys did you work with?
21 A. I worked with a bunch of different
22 attorneys, some of whom are sitting here today, and
23 the others I'm sure were involved as well.
24 Q. Did you work with Mr. Dykhuis on the
25 case?

1 Q. Okay. Today you're being recorded
2 both by video and also stenographically, so we ask
3 that you give verbal responses rather than just
4 head nods or hand gestures.
5 Does that make sense?
6 A. Yes.
7 Q. I'll try to be clear with my
8 questioning. If I'm not clear, you can ask me to
9 clarify my questions, but if you provide an answer,
10 I'll assume that you understood my questions.
11 Does that make sense?
12 A. Sounds good.
13 Q. Your counsel may object at various
14 times today, but you understand that you still need
15 to respond to my questions unless your counsel
16 instructs you not to answer?
17 A. I understand.
18 Q. Okay. I'll take breaks, as we
19 discussed, periodically. If you need a break, at
20 any time, the only thing I ask is that if there's a
21 pending question, you answer that question and we
22 can take a break, okay?
23 A. I understand.
24 Q. Is there any reason why you can't
25 provide truthful and accurate testimony today?

Page 9

1 A. You know, I'm not sure if he was
2 part of helping with the declaration, but I suspect
3 he did.
4 Q. How generally was your declaration
5 in this case prepared?
6 ATTORNEY DYKHUIS: Object to form
7 and also just caution you, Dr. Nathan,
8 don't divulge of substance of any
9 communications with counsel, but you can
10 describe generally.
11 THE WITNESS: It was a -- the
12 declaration was formulated by myself
13 together with assistance of the counsel.
14 BY ATTORNEY DAVIES:
15 Q. Do you recall any of the names of
16 the counsel that assisted with the preparation?
17 ATTORNEY DYKHUIS: Object to form.
18 THE WITNESS: There were a number
19 of people on the email chain, and I'm not
20 sure who exactly assisted. It seems like
21 it was a combined effort on the part of
22 counsel.
23 BY ATTORNEY DAVIES:
24 Q. Did you have any in-person meetings
25 to prepare your declaration?



3 (Pages 6 to 9)

Page 10

Page 11

1 A. No.
2 Q. Did you draft any portions of your
3 declaration?
4 ATTORNEY DYKHUIS: Object to form.
5 THE WITNESS: Yes, I did.
6 BY ATTORNEY DAVIES:
7 Q. Do you recall, sitting here today,
8 which portions you drafted?
9 A. Most -- or if not all of the medical
10 stuff is what I wrote, primarily.
11 (Exhibit 1 was marked for
12 identification.)
13 Q. Dr. Nathan, I've marked as Exhibit 1
14 a deposition notice entitled Defendant Liquidia,
15 Inc.'s Notice of Deposition of Steven D. Nathan.
16 I'm going to pass that to you. I just ask you
17 because of the weird shape of the table, would you
18 mind passing one copy to counsel all the way
19 around?
20 A. Sure.
21 Q. Thank you very much.
22 Doctor, you should keep the copy with the
23 yellow stickers on it, if that makes sense.
24 A. Yes.
25 Q. And you understand that you're here

1 today testifying in a case between United
2 Therapeutics and Liquidia in which you submitted a
3 declaration; correct?
4 A. Yes.
5 (Exhibit 2 was marked for
6 identification.)
7 Q. So I've marked as Exhibit 2 a
8 document titled "Declaration of Steven D. Nathan,
9 M.D, in support of Plaintiff's motion for
10 preliminary injunction."
11 And, again, I'm going to pass to you one
12 extra copy if you can pass that to Mr. Dykhuis,
13 please.
14 And Dr. Nathan, is Exhibit 2 that I just
15 passed you, is that the copy of the declaration
16 that you submitted in this case?
17 A. I just want to check to see what
18 else is in there.
19 Yes, it is.
20 Q. This copy that I passed you to
21 includes Attachments A, B, and C; correct? And
22 they begin after page 90 of your declaration.
23 A. Attachment A? After 90? This is C
24 at the end. I don't dispute it.
25 Q. Does this appear to be a complete

Page 12

Page 13

1 copy of the report that you submitted in this case?
2 A. It does appear to be it.
3 Q. Could you turn to what would be
4 page 90. It's the last page of your report before
5 the attachments.
6 A. (Witness complies with request.)
7 Yes.
8 Q. And that's your signature on
9 page 90?
10 A. Yes, it is.
11 Q. And it's dated February 26, 2024?
12 A. Yes.
13 Q. With respect to this declaration,
14 are there any mistakes or errors in this
15 declaration that you're aware of sitting here
16 today?
17 A. There must be one or two typos that
18 I saw subsequently. For example, an "and" instead
19 of "an" and one of the footnotes there's also a
20 typo.
21 Q. Could you point me to the footnote
22 that's a typo.
23 A. Oh, gosh. Give me a minute. Okay.
24 Sorry it's taking a while. I have a lot of
25 documents to go through.

1 I didn't see it in the first run. If I
2 may, may I ask counsel to point me to where there's
3 that footnote? Would that be okay, or do I have to
4 keep looking?
5 Q. I would not object to asking your
6 counsel which one it is.
7 ATTORNEY DYKHUIS: I think you
8 might be thinking of Paragraph 119.
9 (Pause)
10 THE WITNESS: So that's page 43
11 you're talking about?
12 BY ATTORNEY DAVIES:
13 Q. Do you believe the error is in
14 either footnotes 99, 100, or 101 on page 43,
15 Doctor?
16 A. No, I think it's another footnote.
17 Q. Okay.
18 A. I apologize.
19 Q. Do you recall the nature of the
20 error, Dr. Nathan?
21 A. It was just really a minor error --
22 Q. Okay.
23 A. -- that just had an incorrect
24 reference to what the subject matter was. It
25 wasn't really pertinent to anything, really. And

Page 14	Page 15
<p>1 I'm not sure if we go through this if I might come 2 across it as we go through. 3 Q. So other than an "and" rather than 4 and "an" and a minor footnote -- a minor typo in a 5 footnote, are there any other errors or typos that 6 you're aware of in your report today? 7 A. None that I'm aware of. 8 Q. Okay. Can you go to Attachment B of 9 your declaration, Exhibit 2. 10 A. (Witness complies with request.) 11 Q. Just let me know once you're there. 12 A. Attachment B is one page, and I see 13 here that I had said four. I might be mistaken. 14 There might have been one many, many years ago that 15 wasn't picked up. I apologize if that is an 16 oversight on my part. 17 Q. The one many, many years ago, was 18 that a -- did you act as an expert in that case 19 many, many years ago? 20 A. I believe so, yes. 21 Q. Okay. Did that case concern 22 pulmonary hypertension? 23 A. I don't recall the details of the 24 case. 25 Q. Do you recall if that was a patent</p>	<p>1 litigation case? 2 A. It was not a patent litigation case. 3 Q. Okay. What type of case was it, 4 generally? 5 A. It was an medicolegal case. 6 Q. Like a med malpractice? 7 A. Yes. 8 Q. In the Genentech v. Aurobindo Pharma 9 case, that's the first one in your prior testimony, 10 did you author an expert report in that case? 11 A. I believe I did, yes. 12 Q. Were you deposed in that case? 13 A. As I recall, I was. 14 Q. Did you testify at trial in that 15 case? 16 A. That I did, yes. 17 Q. And I'm not asking for confidential 18 information, but can you tell me generally what the 19 subject matter of your testimony was in that case? 20 A. It was regarding the validity of the 21 patent over which the companies were having -- were 22 contesting. 23 Q. And which of the parties were you 24 consulting with? 25 A. I was consulting on behalf of</p>
Page 16	Page 17
<p>1 Genentech. 2 Q. So on behalf of the patentee? 3 A. That's correct. 4 ATTORNEY DYKHUIS: Object to form. 5 Q. Do you remember generally the 6 subject matter of the patent at issue in that case? 7 A. I do. 8 Q. And what was it? 9 A. There were two clauses pertaining to 10 checking liver function tests and another clause 11 pertaining to drug-drug interactions. 12 Q. Is the Christopher -- the next case 13 on your list, the Christopher Mee versus Robertson 14 [sic], is that a medical malpractice case? 15 ATTORNEY DYKHUIS: Object to the 16 form. 17 THE WITNESS: It is. 18 BY ATTORNEY DAVIES: 19 Q. And the Washington verus American 20 Homes, what type of case was that? 21 A. I don't recall exactly the details 22 of that. It might have been, but I'm not sure, 23 just by judging by the names, there was one case I 24 was involved in where the -- I guess it would be 25 the plaintiff had some exposure to chlorine. And</p>	<p>1 just by virtue of the names here, it might have 2 been that one, but I'm not certain. 3 Q. So other than the four cases that 4 we've talked about, any other cases that you've 5 testified either by deposition or at trial that you 6 can recall sitting here today? 7 ATTORNEY DYKHUIS: Object to form. 8 THE WITNESS: As I mentioned, 9 there might have been another one way 10 back, and I just don't remember the 11 details of that. It wasn't patent 12 litigation. It was not medical 13 malpractice. 14 BY ATTORNEY DAVIES: 15 Q. Okay. Can you go, Doctor, to 16 Exhibit A, please. I'm sorry, Attachment A of your 17 declaration. Apologies. 18 A. Attachment A looks like my CV. 19 Q. Is this the most current copy of 20 your CV? 21 A. I keep my CV updated as publications 22 and talks come out. So my CV is updated, can be 23 weekly, depending on what's going on. There 24 haven't been substantive changes to my CV. 25 Q. Did you update this CV after being</p>

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Page 19

1 contacted by counsel for United Therapeutics in
2 this case?
3 ATTORNEY DYKHUIS: Object to form.
4 THE WITNESS: As I say, I'm
5 constantly updating it depending on what
6 I'm doing. And so whenever I'm contacted
7 to forward my CV, I forward the most
8 recent copy of it.
9 BY ATTORNEY DAVIES:
10 Q. Do you recall, sitting here today,
11 whether you updated it after being contacted by
12 counsel for UTC regarding work in this case?
13 ATTORNEY DYKHUIS: Object to form.
14 THE WITNESS: Yes, I do, because I
15 know that I've had papers accepted or
16 published. When I have a paper accepted
17 or published, I'll go back to my CV and
18 update it.
19 BY ATTORNEY DAVIES:
20 Q. This CV was updated in -- on
21 January 17 of 2024. Is that right?
22 A. That's the date on the CV.
23 Q. Okay.
24 A. So that was -- whenever I was
25 contacted, that was the last time I updated it, so

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1 had nothing to input to update it.
2 Q. Understood. Thank you.
3 Can you go to page 2, please, Dr. Nathan.
4 A. I'm on page 2.
5 Q. And it describes your postgraduate
6 education at the top of the CV. Is that correct?
7 A. That's correct.
8 Q. Can you describe what you consider
9 to be your areas of specialty with regard to
10 medical practice?
11 ATTORNEY DYKHUIS: Object to form.
12 THE WITNESS: My areas of
13 specialty would be pulmonary and critical
14 as well as lung transplantation with
15 subsequent initial expertise in
16 interstitial lung disease, pulmonary
17 hypertension, in other 25 of advanced
18 lung disease.
19 BY ATTORNEY DAVIES:
20 Q. Doctor, I think you said "with
21 subsequent initial expertise in interstitial lung
22 disease and pulmonary hypertension."
23 A. Additional.
24 Q. Subsequent additional expertise.
25 Was that your testimony?

1 this is the most current iteration of my CV when I
2 was asked for it.
3 Q. So United Therapeutics would have
4 contacted you before February 17, 2024?
5 ATTORNEY DYKHUIS: Object to form.
6 THE WITNESS: Regarding this case
7 do you mean?
8 BY ATTORNEY DAVIES:
9 Q. Correct, yes.
10 A. I don't recall being contacted
11 previously by United Therapeutics.
12 Q. I apologize. I may have misheard
13 your prior testimony, but I thought you said that
14 you had updated this after being contacted by
15 counsel for United Therapeutics.
16 ATTORNEY DYKHUIS: Object to form.
17 BY ATTORNEY DAVIES:
18 Q. For this case.
19 A. No.
20 Q. You did not.
21 A. I got contacted, to the best of my
22 knowledge, at the beginning of February,
23 Dr. Nathan, please send us your CV. I got back and
24 I sent my CV. The last time I updated was on 1/17.
25 So there might have been a two-week window where I

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1 A. Correct.
2 Q. Okay.
3 A. There's no formal training for
4 those, but those are areas that I've gravitated
5 towards.
6 Q. And when did you gain this
7 subsequent additional expertise in interstitial
8 lung disease and pulmonary hypertension?
9 A. It's accrued over the years.
10 There's no formal training for interstitial lung
11 disease and pulmonary hypertension, at least that
12 wasn't in my day.
13 But I've been involved in pulmonary
14 hypertension since my fellowship at Cedar Sinai,
15 which was the referral center for patients with
16 primary pulmonary hypertension at that time. So
17 I've been seeing patients with pulmonary
18 hypertension since the start of my fellowship,
19 which was in 1988, if not before. I did see some
20 cases as well as a resident.
21 Q. Are you currently employed?
22 A. Yes, I am.
23 Q. And where are you currently
24 employed?
25 A. I'm employed at Inova Fairfax



6 (Pages 18 to 21)

Page 22	Page 23
<p>1 Hospital.</p> <p>2 Q. And what is your position at Inova?</p> <p>3 A. I'm the medical director of the</p> <p>4 advanced lung disease and lung transplant program.</p> <p>5 Q. In your CV it identifies a medical</p> <p>6 director position at Inova Fairfax that began in</p> <p>7 May 2018.</p> <p>8 Do you see that?</p> <p>9 A. Yes.</p> <p>10 Q. Okay. And then it says "inactive."</p> <p>11 A. Yes.</p> <p>12 Q. What does "inactive" mean in your</p> <p>13 CV?</p> <p>14 A. Inova has gone through various</p> <p>15 iterations of how they want to organize pulmonary.</p> <p>16 And initially the pulmonary service line asked us</p> <p>17 to direct, to reorganize. And so the service line</p> <p>18 concept went away.</p> <p>19 Q. Do you have any academic positions</p> <p>20 other than your employment at Inova Fairfax?</p> <p>21 A. I have an employment as professor of</p> <p>22 medical education at University of Virginia.</p> <p>23 Q. Any other academic appointments?</p> <p>24 A. Not at this time.</p> <p>25 Q. Any other employers other than Inova</p>	<p>1 Fairfax currently?</p> <p>2 A. No.</p> <p>3 Q. It also has a position as a</p> <p>4 professor of medical education at the University of</p> <p>5 Virginia. Are you still involved with that?</p> <p>6 A. Yeah, that's the appointment that I</p> <p>7 just mentioned.</p> <p>8 Q. Okay. There is also a professional</p> <p>9 professor of medicine position at Virginia</p> <p>10 Commonwealth University.</p> <p>11 A. Yes.</p> <p>12 Q. Are they two positions, or are they</p> <p>13 the same thing?</p> <p>14 A. That probably should read as ended,</p> <p>15 because what happened was that Inova has</p> <p>16 affiliations with VCU Medical School, and at that</p> <p>17 time I was professor of medicine at VCU. And then</p> <p>18 they changed their medical school affiliation to</p> <p>19 UVA, and that's when I got the subsequent</p> <p>20 appointment.</p> <p>21 So effectively -- and I apologize, it's</p> <p>22 very hard to keep everything up to date -- that</p> <p>23 that should have ended at the same time that the</p> <p>24 UVA appointment started.</p> <p>25 Q. My CV is about four pages long, and</p>
Page 24	Page 25
<p>1 I don't even keep that accurate so I have no</p> <p>2 doubt that it's more difficult for you to do so.</p> <p>3 In your current position at Inova, can you</p> <p>4 describe to me generally your responsibilities in</p> <p>5 that position.</p> <p>6 A. I oversee the advanced lung disease</p> <p>7 and lung transplant program. In the context of</p> <p>8 their advanced lung disease program, we had various</p> <p>9 other programs, including a pulmonary hypertension</p> <p>10 program, which is accredited by the Pulmonary</p> <p>11 Hypertension Association as one of the care</p> <p>12 centers.</p> <p>13 We have an interstitial lung disease</p> <p>14 program that's accredited by the Pulmonary Fibrosis</p> <p>15 Foundation. We have a cystic fibrosis program</p> <p>16 that's accredited by the CF Foundation, and we have</p> <p>17 a comprehension saccharidosis program, that's</p> <p>18 accredited by the World's Association for</p> <p>19 Saccharidosis and Other Granulomatous Diseases.</p> <p>20 Q. Do you still -- maybe I used the</p> <p>21 wrong word there.</p> <p>22 Do you still see patients in the clinic?</p> <p>23 A. Yes, I do.</p> <p>24 Q. Okay. And how many days a week are</p> <p>25 you working in the clinic seeing patients?</p>	<p>1 A. I work -- I work 10 and a half days</p> <p>2 in the clinic seeing patients, but then sometimes</p> <p>3 I'll add patients on if they need to be seen on an</p> <p>4 emergency or I want to squeeze them in, I might see</p> <p>5 them on a day that I'm not in the clinic.</p> <p>6 Q. And is that split with your clinical</p> <p>7 practice, has that been true since about 2018?</p> <p>8 ATTORNEY DYKHUIS: Object to form.</p> <p>9 THE WITNESS: That's approximately</p> <p>10 correct. I don't remember exactly when I</p> <p>11 went to 2.5 or what effectively works out</p> <p>12 at a .5 clinical FD. I don't recall</p> <p>13 exactly when that was.</p> <p>14 BY ATTORNEY DAVIES:</p> <p>15 Q. How many pulmonary hypertension</p> <p>16 patients are currently under your care?</p> <p>17 A. Since it follows, in the range of</p> <p>18 about 400 to 500 patients with group 1 pulmonary</p> <p>19 arterial hypertension. And then we have</p> <p>20 approximately 11 to 1200 patients with interstitial</p> <p>21 lung disease, many of whom have pulmonary</p> <p>22 hypertension associated with interstitial lung</p> <p>23 disease.</p> <p>24 There are a number of providers, but I see</p> <p>25 a good proportion of patients with pulmonary</p>

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1 arterial hypertension, patients with interstitial
2 lung disease and patient with IOVPH.
3 Q. Can you go to page 5 of your CV.
4 A. (Witness complies with request.)
5 I'm on page 5.
6 Q. And it looks like it actually begins
7 on page 4, there's a heading entitled "Committees."
8 Do you see that?
9 A. Yes.
10 Q. And it appears to include your
11 membership on steering committees for various
12 clinical studies. Is that correct?
13 A. That's correct.
14 Q. If you go to the top of page 5,
15 there's a study, the very first one, 2016 to 2021,
16 steering committee member of phase 2B study of
17 Sildenafil added to pirfenidone in advanced IPF in
18 an immediate or high probability of Group 3 PH.
19 Do you see that?
20 A. I do.
21 Q. Do you recall the study name?
22 A. There was an acronym that went with
23 it. I don't recall what that acronym was.
24 Q. Was there a publication that issued
25 from that study?

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1 endpoint. On rare occasions there could
2 be two primary endpoints.
3 BY ATTORNEY DAVIES:
4 Q. If you go down -- I'll find it. If
5 you go down to the next -- I'm sorry.
6 If you go down to the next entry, there's a
7 steering committee member for RIN PH 201, the
8 INCREASE study.
9 Do you see that?
10 A. I do.
11 Q. Okay. When was the steering
12 committee formed for INCREASE?
13 A. Based on my CV, it appeared that it
14 was in 2016.
15 Q. So that indicates the beginning of
16 your involvement as a steering committee member?
17 ATTORNEY DYKHUIS: Object to form.
18 THE WITNESS: Based on my CV, I
19 believe that would be correct.
20 BY ATTORNEY DAVIES:
21 Q. Who else was a member of the
22 steering committee for INCREASE?
23 A. There were two other members:
24 Dr. Aaron Waxman and Dr. Richard Tapson.
25 Q. Can you repeat the second member of

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1 ATTORNEY DYKHUIS: Object to form.
2 THE WITNESS: Yes, it was. I
3 believe it was published in the Advanced
4 Respiratory Medicine.
5 BY ATTORNEY DAVIES:
6 Q. Were you one of the authors on that
7 paper?
8 A. As I recall, I was the second author
9 on that paper.
10 Q. Do you recall generally the outcome
11 of that study?
12 A. The study was a negative study.
13 Q. In what sense was it a negative
14 study?
15 A. It didn't meet its primary endpoint.
16 Q. What was the primary endpoint?
17 A. As I recall, it was time to clinical
18 worsening.
19 (Reporter clarification)
20 Q. Were there any other primary
21 endpoints?
22 ATTORNEY DYKHUIS: Object to form.
23 THE WITNESS: There were -- not at
24 the primary endpoints. Typically in the
25 studies you only have one primary

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1 the steering committee for INCREASE, Doctor.
2 A. Victor Tapson.
3 Q. Victor Tapson?
4 A. Yes.
5 Q. What was the responsibility of the
6 steering committee with respect to the design of
7 the INCREASE?
8 ATTORNEY DYKHUIS: Object to form.
9 THE WITNESS: We were all involved
10 in coming up with the design in terms of
11 inclusion, exclusionary criteria, and
12 endpoints, as I best recall.
13 BY ATTORNEY DAVIES:
14 Q. What was your contribution, in your
15 view, to the design of the INCREASE study?
16 A. I don't remember my individual
17 contribution. We're talking, I guess, nine years
18 ago now. I'm sure that I had some kind of
19 contribution, and at the end of the day it was a
20 consensus in terms of how the study was designed.
21 Q. Other than the three steering
22 committee members, did anyone else have involvement
23 in the study design of the INCREASE study?
24 ATTORNEY DYKHUIS: Object to form.
25 THE WITNESS: Yes, there were.

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1 There were representatives from United
2 Therapeutics. It was their study, and
3 Peter Smith was one of them. C.Q. Quinn,
4 who was the biostatistician, was also
5 involved in terms of figuring out how
6 we're going to analyze the data
7 statistically.
8 BY ATTORNEY DAVIES:
9 Q. Anyone else you recall?
10 A. I don't remember. I made a mistake.
11 I said nine years ago. My math was incorrect.
12 It's eight years ago.
13 Q. No problem. We all get grades today
14 because we lost an hour last night.
15 A. We lost what?
16 Q. We lost an hour last night.
17 A. I thought you were going to say that
18 you were a Duke fan.
19 Q. Do you recall anything about
20 Dr. Aaron Waxman's contribution to the design of
21 the INCREASE study?
22 A. I do not.
23 Q. Do you recall anything about
24 Dr. Victor Tapson's contribution to the design of
25 the INCREASE study?

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1 who were enrolled in the INCREASE study.
2 Q. You said it's corresponding to a
3 risk score?
4 A. Risk score. Risk stratify the
5 patients who have pulmonary hypertension who were
6 in the study.
7 Q. Are there any post hoc analyses
8 concerning FVC?
9 A. There was one that was published in
10 Advanced Respiratory Medicine.
11 Q. Are you an author on that paper?
12 A. Yes.
13 Q. Why was there a post hoc analysis of
14 the INCREASE study done with respect to FVC?
15 ATTORNEY DYKHUIS: Object to form.
16 THE WITNESS: The FVC looked at --
17 at baseline and then at the end of the
18 study, and what we saw appeared to be a
19 difference favoring inhaled treprostinil
20 in terms of preservation of the FVC in
21 comparison to the placebo arm, and that
22 was the basis for the post hoc analysis.
23 BY ATTORNEY DAVIES:
24 Q. So with respect to the initial
25 INCREASE study, you said you saw what appeared to

1 A. I do not. As I said, we've all
2 contributed in our own way, and then the study
3 design ultimately was a consensus against everyone,
4 including the folks from United Therapeutics.
5 Q. Okay. There's no end date for the
6 steering committee membership for the INCREASE
7 study in your CV. Is that steering committee still
8 active?
9 A. We don't meet as a steering
10 committee. However, where there is activity are
11 various post hoc analyses of the INCREASE study
12 which remain ongoing, and that's probably the
13 reason that I haven't closed it out.
14 Q. Are there any current post hoc
15 analyses of INCREASE that are ongoing?
16 ATTORNEY DYKHUIS: Object to form.
17 THE WITNESS: Yes, they there.
18 BY ATTORNEY DAVIES:
19 Q. And what are they?
20 A. We've done numerous post hoc
21 analyses. There's one paper that's in submission
22 about treating patients with more mild pulmonary
23 hypertension as the subject of analysis.
24 There is another paper being developed
25 pertaining to a risk score in terms of the patients

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1 be a difference; is that correct?
2 ATTORNEY DYKHUIS: Object to form.
3 THE WITNESS: Correct.
4 BY ATTORNEY DAVIES:
5 Q. Was in your opinion -- with the
6 initial analysis of INCREASE, was there a
7 statistically significant difference in FVC with
8 inhaled treprostinil treatment?
9 ATTORNEY DYKHUIS: Object to form.
10 THE WITNESS: As best I recall,
11 there was based on percent predicted, but
12 not absolute in terms of milliliters.
13 However, those became significant when we
14 looked at various subgroups, including
15 those patients with idiopathic
16 interstitial pneumonia and a further
17 subgroup of those patients, the patients
18 with idiopathic pulmonary fibrosis.
19 BY ATTORNEY DAVIES:
20 Q. So at least with the initial
21 INCREASE study, there was not a significant
22 difference in FVC with treprostinil treatment
23 across all patients; correct?
24 ATTORNEY DYKHUIS: Object to form.
25 THE WITNESS: There was. There

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1 are two ways you can look at the FVC.
2 You can look at the absolute number,
3 which is how many ccs or milliliters, or
4 you can look at it as a percent
5 predicted, and there was a statistical
6 difference when you looked at it based on
7 percent predicted.

8 BY ATTORNEY DAVIES:

9 Q. Which of those two measures or
10 analyses do you feel is more accurate?

11 ATTORNEY DYKHUIS: Object to form.

12 THE WITNESS: They are both
13 accurate. They just tell you different
14 ways of looking at the FVC.

15 BY ATTORNEY DAVIES:

16 Q. What's the significance to you as a
17 clinician where one method produces a statistically
18 significant difference and the other does not?

19 ATTORNEY DYKHUIS: Object to form.

20 THE WITNESS: It really doesn't
21 make a difference to me how I look at the
22 data, to be quite honest.

23 BY ATTORNEY DAVIES:

24 Q. What do you mean, it doesn't make a
25 difference to you how you look at the data?

1 A. I look at the compendium of the
2 data. One is positive, one is negative. I
3 wouldn't say "negative." It probably was a trend;
4 I don't remember what the P value was. But the
5 study wasn't powered to look at the FVC.

6 So it's an interesting observation that
7 remained to be further validated and that is
8 currently ongoing.

9 Q. Was the post hoc analysis powered to
10 look at FVC?

11 ATTORNEY DYKHUIS: Object to the
12 form.

13 THE WITNESS: No, you can't power
14 a study retrospectively.

15 BY ATTORNEY DAVIES:

16 Q. Why -- whose decision was it to do
17 the post hoc analysis for FVC?

18 ATTORNEY DYKHUIS: Object to form.

19 THE WITNESS: It was an easy group
20 decision, because we saw the signal when
21 we looked at the FVC, and it was somewhat
22 surprising and unexpected.

23 FVC was initially looked at as a
24 safety measure. We're giving a
25 medication by the inhaled drug to

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1 patients who had interstitial lung
2 disease, and we didn't know if we would
3 be hurting these patients because they
4 are very different from Group 1 PAH
5 patients that have parenchymal lung
6 disease and getting anything inhaled is
7 the possibility you could harm them. And
8 that was why it was labeled as a safety
9 endpoint.

10 BY ATTORNEY DAVIES:

11 Q. Sitting here today, are you
12 confident that administration of inhaled
13 treprostinil produced a statistically significant
14 improvement in FVC in the INCREASE study?

15 ATTORNEY DYKHUIS: Object to form.

16 THE WITNESS: If you look at
17 percent predicted, I'd have to go to the
18 paper, if you have it, just to make sure
19 what I'm saying is the truth. But as
20 best I recall, there was a statistically
21 significant difference. So I'm confident
22 with that.

23 I would need to look at the paper
24 to make sure that what I'm telling you is
25 correct, but that's the best of my

1 recollection. So I'm confident in the
2 analyses that were done in the post hoc
3 analysis.

4 BY ATTORNEY DAVIES:

5 Q. And what about the initial analyses
6 in the absence of the post hoc analyses? In your
7 opinion, does that support a statistically
8 significant improvement in FVC, or was it uncertain
9 with the initial analysis?

10 ATTORNEY DYKHUIS: Object to form.

11 THE WITNESS: I believe the
12 initial analysis showed the same thing.
13 It's just that in the post hoc analysis
14 we dug deeper into it, and that's when we
15 did the subgroup analyses.

16 BY ATTORNEY DAVIES:

17 Q. So to the best of your recollection,
18 with respect to FVC, INCREASE showed a significant
19 difference in percent predicted. Is that correct?

20 ATTORNEY DYKHUIS: Object to form.

21 THE WITNESS: In favor of inhaled
22 treprostinil versus placebo.

23 BY ATTORNEY DAVIES:

24 Q. Is that correct?

25 A. Correct.

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1 Q. But with respect to absolute
2 improvements in FVC, there was not a significant
3 difference following treatment with inhaled
4 treprostinil in the INCREASE study; correct?
5 ATTORNEY DYKHUIS: Object to form.
6 THE WITNESS: I wouldn't regard it
7 as improvement. I believe that's what
8 you said. It was placebo-corrected
9 difference.
10 BY ATTORNEY DAVIES:
11 Q. So there was not a significant
12 difference in absolute FVC in the INCREASE study;
13 correct?
14 ATTORNEY DYKHUIS: Object to form.
15 THE WITNESS: That's to the best
16 of my recollection.
17 BY ATTORNEY DAVIES:
18 Q. Okay.
19 A. For the patients as a whole, but for
20 the subgroups it was.
21 Q. When was the -- when was the
22 post hoc analysis on FVC, when was that started?
23 ATTORNEY DYKHUIS: Object to form.
24 THE WITNESS: I don't recall the
25 exact date. I think that it was probably

1 2021 sometime, early 2021, but I don't
2 recall the exact date. Sorry.
3 BY ATTORNEY DAVIES:
4 Q. No problem.
5 You mentioned that the INCREASE study was
6 designed by a consensus of the five committee
7 members that you can recall; correct?
8 ATTORNEY DYKHUIS: Objection to
9 form.
10 THE WITNESS: It was the three
11 steering committee members and the
12 sponsor.
13 BY ATTORNEY DAVIES:
14 Q. Okay. And the protocol for INCREASE
15 was designed as a consensus of the three committee
16 members; is that correct?
17 ATTORNEY DYKHUIS: Object to form.
18 THE WITNESS: Together with the
19 sponsor.
20 BY ATTORNEY DAVIES:
21 Q. Okay. Do you remember any input
22 that the sponsor offered UTC -- strike that. Let
23 me start over.
24 Can you recall sitting here today
25 any specific -- let me try it one more time.

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1 Sitting here today, can you recall any
2 specific input or contribution of United
3 Therapeutics's representatives to the design of the
4 INCREASE study?
5 ATTORNEY DYKHUIS: Objection to
6 form.
7 THE WITNESS: They had a
8 substantial contribution. The way it
9 worked is that we were sent a cursory
10 protocol, and then we provided input in
11 terms of, you know, maybe think about
12 this, maybe think about that, but they
13 really provided the foundation for the
14 study.
15 BY ATTORNEY DAVIES:
16 Q. Do you recall sitting here today any
17 belief by the study members -- strike that.
18 Do you recall sitting here today any belief
19 by the steering committee members that the study
20 would not be successful?
21 ATTORNEY DYKHUIS: Object to the
22 form.
23 THE WITNESS: Yes. I had my
24 doubts that it would be successful for
25 sure.

1 BY ATTORNEY DAVIES:
2 Q. Why did you believe it would not --
3 well, why did you have doubts regarding the success
4 of the study?
5 A. Because it had been no prior
6 randomized controlled study in PH-ILD demonstrating
7 success, and personally I had just come off being
8 the chair of the steering committee of the RISE IP
9 study, which was riociquat for the same indication,
10 PH-ILD, and not only was that a negative study, but
11 it was a harmful study.
12 Q. Do you recall Dr. Waxman expressing
13 any belief that the study would not be successful?
14 ATTORNEY DYKHUIS: Objection,
15 form.
16 THE WITNESS: I don't recall that.
17 BY ATTORNEY DAVIES:
18 Q. Okay. Do you recall Dr. Victor
19 Tapson expressing any belief that the study would
20 not be successful?
21 ATTORNEY DYKHUIS: Object to the
22 form.
23 THE WITNESS: I don't recall that.
24 BY ATTORNEY DAVIES:
25 Q. Okay. Regarding your feelings about

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1 the study in your past experience from the RISE
2 study, why were you willing to be a member of the
3 steering committee, given your past experience with
4 RISE?

5 ATTORNEY DYKHUIS: Objection to
6 the form.

7 THE WITNESS: I was asked to be a
8 steering committee member, and I valued
9 the opportunity. And we have many
10 negative studies in medicine that have
11 subsequently been followed by positive
12 studies.

13 So I think the history of medicine
14 is such that if you have one negative
15 study, you don't necessarily give up. If
16 you look at another disease that I deal
17 with, idiopathic pulmonary fibrosis, for
18 which there are two anti-fibrotics that
19 are approved, there are about 10 RCTs,
20 randomized studies, prior to that before
21 those came back positive.

22 So, you know, if we just gave up
23 on all treatments, we wouldn't have
24 anything for cancer today.
25

1 BY ATTORNEY DAVIES:

2 Q. So when during the development of
3 the INCREASE study did you become optimistic that
4 it would succeed?

5 ATTORNEY DYKHUIS: Object to the
6 form.

7 THE WITNESS: When I heard the
8 results.

9 BY ATTORNEY DAVIES:

10 Q. So until you heard the results of
11 the INCREASE study, you were not optimistic that
12 the study would succeed?

13 ATTORNEY DYKHUIS: Object to the
14 form.

15 THE WITNESS: I had my doubts.

16 BY ATTORNEY DAVIES:

17 Q. And when did you first hear the
18 results of the INCREASE study?

19 ATTORNEY DYKHUIS: Objection to
20 form.

21 THE WITNESS: It was sometime
22 towards the end of February of 2020.

23 BY ATTORNEY DAVIES:

24 Q. Do you recall who communicated those
25 results to you?

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1 A. Peter Smith.

2 Q. Who is Peter Smith?

3 A. He was one of the two UT members,
4 and he led the study from the sponsor standpoint
5 for United Therapeutics.

6 Q. Do you recall United Therapeutics
7 ever expressing any skepticism that the INCREASE
8 study would not be successful?

9 ATTORNEY DYKHUIS: Objection to
10 form.

11 THE WITNESS: No.

12 BY ATTORNEY DAVIES:

13 Q. The communication in February 2020
14 that you received from Peter Smith regarding the
15 data, was the study data locked at that point, or
16 what stage in data collection was ongoing at that
17 point?

18 ATTORNEY DYKHUIS: Objection to
19 form.

20 THE WITNESS: The study was
21 locked, and they had done the analysis of
22 the primary endpoint, and I believe at
23 that time some of the secondary endpoints
24 as well.
25

1 BY ATTORNEY DAVIES:

2 Q. So by the time you got -- you heard
3 the results from Peter Smith, the study had been
4 locked and there had been analysis on both the
5 primary and secondary endpoints as well; correct?

6 ATTORNEY DYKHUIS: Objection to
7 form.

8 THE WITNESS: As best I recall.

9 BY ATTORNEY DAVIES:

10 Q. And this was the first time that you
11 were optimistic that the study would be successful;
12 correct?

13 ATTORNEY DYKHUIS: Objection to
14 form.

15 THE WITNESS: That's correct.

16 BY ATTORNEY DAVIES:

17 Q. Did Leigh Peterson contribute to the
18 design or conduct of the INCREASE study?

19 ATTORNEY DYKHUIS: Object to form.

20 THE WITNESS: I don't recall
21 specifically that she could well have. I
22 suspect that there was a lot of
23 communication behind the scenes that the
24 steering committee members were not
25 necessarily privy to.

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1 BY ATTORNEY DAVIES:
2 Q. To your knowledge, who is Leigh
3 Peterson?
4 ATTORNEY DYKHUIS: Object to form.
5 THE WITNESS: She's an employee of
6 United Therapeutics.
7 BY ATTORNEY DAVIES:
8 Q. Do you know generally what her
9 responsibilities were, if any, with respect to the
10 INCREASE study?
11 A. I do not.
12 Q. Did you ever have any conversations
13 with Leigh Peterson regarding the INCREASE study?
14 A. I don't recall any.
15 Q. Do you know if Peter Smith had any
16 contribution to the design or conduct of the
17 INCREASE study?
18 ATTORNEY DYKHUIS: Object to the
19 form.
20 THE WITNESS: I'm pretty sure he
21 did without knowing a hundred percent.
22 He led the study, so I think it's
23 reasonable to assume that he had some
24 essential contributions, but I can't tell
25 you for sure.

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1 committee for the PERFECT study?
2 A. It was myself, Vic Tapson -- Victor
3 Tapson, Aaron Tapson, and there was an additional
4 member, Todd Bull, B-u-I-I.
5 Q. And is that steering committee still
6 active as well?
7 ATTORNEY DYKHUIS: Object to the
8 form.
9 THE WITNESS: The paper pertaining
10 to that study is currently in
11 development, and so with regards to
12 fine-tuning the paper, the steering
13 committee still has input into that.
14 The study got stopped early for
15 lack of efficacy and a signal of
16 potential harm, and this was inhaled
17 trepostinil in patients, with COPD.
18 BY ATTORNEY DAVIES:
19 Q. Is PH due to COPD, is that a
20 Group 3?
21 A. That's correct.
22 ATTORNEY DYKHUIS: Object to the
23 form.
24 Q. I'm sorry. I want to just ask, I'll
25 try to rephrase that a little bit better.

1 BY ATTORNEY DAVIES:
2 Q. What about Chung Kun Dang? Did he
3 have any role in the conduct or design of the
4 INCREASE study?
5 ATTORNEY DYKHUIS: Object to form.
6 THE WITNESS: Yes, he did, because
7 he's the biostatistician that helps to
8 come up with the statistical analysis
9 plan.
10 BY ATTORNEY DAVIES:
11 Q. Below -- going back to your CV,
12 Doctor, I'm sorry, your CV is Attachment A to your
13 declaration, which is Exhibit 2.
14 The next steering committee membership I
15 wanted to ask you about began in 2016, steering
16 committee member for RIN PH 203 study.
17 Do you see that?
18 ATTORNEY DYKHUIS: Object to the
19 form.
20 THE WITNESS: Yes, I do.
21 BY ATTORNEY DAVIES:
22 Q. Does that have a study name?
23 A. Yes, it does. That is known as the
24 PERFECT study.
25 Q. Who else was on the steering

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1 Is pulmonary hypertension due to chronic
2 obstructive -- strike that.
3 How many -- you're aware that there's five
4 groups of pulmonary hypertension; correct?
5 A. That's correct.
6 Q. Okay. Which of those five groups
7 does pulmonary hypertension due to chronic
8 obstructive pulmonary disease fall into?
9 A. Group 3.
10 Q. Do you know whether United
11 Therapeutics was still investigating the use of
12 inhaled treprostinil for PH COPD?
13 A. I don't believe they are.
14 Q. Why do you believe that that study
15 failed?
16 ATTORNEY DYKHUIS: Objection to
17 form.
18 THE WITNESS: I don't know why the
19 study failed. There are many moving
20 parts to a successful study design. I
21 think it just underscores a point that
22 not all forms of lung disease which are
23 conflicted by pulmonary hypertension
24 necessarily behave the same or respond
25 the same to therapy.

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BY ATTORNEY DAVIES:

Q. If you turn to page 8, there's a list of your publications that begins on page 8.

A. Okay.

Q. And I believe you testified that you're not aware of any significant additions to that list of publications.

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: There have been some publications that have been added. Maybe one or two. I can't recall exactly right now.

BY ATTORNEY DAVIES:

Q. Are there any that you're aware of that are or that concern the use of treprostinil?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: I'll have to go and see what the last entry is here.

No, I don't believe -- let me just double-check, I apologize. I don't believe that there are any new publications pertaining to inhaled -- treprostinil.

BY ATTORNEY DAVIES:

Q. If you turn to page 29 of your CV,

and this appears to be a list of publications in submission or preparation. Is that correct?

A. Correct.

ATTORNEY DYKHUIS: Object to form.

Q. We talked about the post hoc analysis with regard to FVC that was done for the INCREASE study.

Do you recall that?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: Yes.

BY ATTORNEY DAVIES:

Q. Is 18 the in-preparation publication of those results and analysis?

A. No. This isn't the FVC. That was the question you had.

Q. Correct.

A. I can direct you to that one, because that's not in preparation. That has been published.

It's publication number 137.

Q. What is the post hoc analysis of INCREASE that's described at 18 on page 29 of your CV?

A. There's no mention of efficacy that I can see in Number 18.

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Q. And I'm sorry, Doctor, I may not have been clear. What is the post hoc analysis of INCREASE that's described at Number 18 on page 29 of your CV?

A. That was looking at outcomes in patients with less severe pulmonary hypertension. It didn't pertain to the FVC.

Q. And why did you decide to do this post hoc analysis that's described in 18?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: There have been many ideas that have come out with this very rich dataset, and that was one of them. Despite the overwhelmingly positive results, that does still exist in the community skepticism around the INCREASE study, and specifically with enough patients with more mild pulmonary hypertension are responders.

And that was a reason to do an analysis into patients who had more mild pulmonary hypertension just to drill down on all the potential benefits that you could see with if patients with mild pulmonary hypertension were treated.

BY ATTORNEY DAVIES:

Q. And what were the results of that post hoc analysis with respect to this more mild PH patient population?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: Once you do post hoc analyses, the numbers get smaller. And when the numbers get smaller, it becomes much more difficult to show statistical significance.

But the point estimates in what we call the hazard ratios for clinical worsening did appear to favor inhaled treprostinil, as well as the point estimate for the risk of acute exacerbations did fail to -- I'm sorry, did favor inhaled treprostinil. It didn't reach statistical significance, and then the change in the biomarker were used, which is called the NT-ProBNP also showed a favorable effect in the group that got inhaled treprostinil. And I think the NT-ProBNP hits statistical significance.

BY ATTORNEY DAVIES:

Q. Did you examine change in six-minute

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1 walk distance analysis in this post hoc analysis?
2 A. The change in the six-minute walk
3 distance had been reported in the primary INCREASE
4 publication in patients with more mild pulmonary
5 hypertension. Honestly, I don't recall how much we
6 reported out on the six-minute walk in this
7 post hoc analysis. I think we did.
8 The paper is still in revision at the
9 moment, but without having the paper in front of
10 me, I can't tell you a hundred percent. I'm pretty
11 sure that we must have examined the six minute walk
12 distance.
13 Q. Do you recall whether there was a
14 statistically significant difference in six-minute
15 walk distance in this patient population subgroup
16 with more mild pulmonary hypertension?
17 ATTORNEY DYKHUIS: Object to form.
18 THE WITNESS: Well, if you go back
19 to the primary paper, in the supplement
20 to the primary paper there's an analysis
21 of patients with pulmonary vascular
22 resistances between three and four, and
23 it did not appear to be any effect on the
24 six-minute walk.
25 Hence, the skepticism, and hence

1 the reason we did this deeper dive
2 looking at these other outcome measures
3 which did appear to show benefit in this
4 group of patients.
5 BY ATTORNEY DAVIES:
6 Q. You mentioned, I believe, in one of
7 your earlier responses, Doctor, exacerbations of
8 interstitial lung disease.
9 Did I recall that correctly?
10 A. Yes.
11 Q. What is an exacerbation of
12 interstitial lung disease?
13 A. There's a strict definition for what
14 an exacerbation of interstitial lung disease is and
15 the guidelines for that in terms of worsening
16 infiltrates on chest imaging, worsening shortness
17 of breath over a time period of less than four
18 weeks. Worsening gas exchange and ruling out other
19 causes like infection or heart failure.
20 So it's -- and then if you rule all those
21 out, you're left with an acute exacerbation of
22 interstitial lung disease.
23 Q. With respect to this more mild PH
24 subgroup of patients, was there a statistically
25 significant difference with respect to

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1 exacerbations of interstitial lung disease?
2 ATTORNEY DYKHUIS: Object to form.
3 THE WITNESS: The points estimate
4 was way to the left favorable for inhaled
5 trepostinil. I think that it was
6 something like an 80 percent risk
7 reduction, if I recall the point estimate
8 exactly. Because the numbers were very
9 small, the error bars were very wide and
10 crossed the line of unity so that the
11 post hoc analysis suffered from
12 insufficient numbers to have a definitive
13 answer that the point estimate suggested
14 strongly that there was a substantial
15 benefit.
16 BY ATTORNEY DAVIES:
17 Q. But there was not a statistically
18 significant difference; correct?
19 ATTORNEY DYKHUIS: Objection to
20 form.
21 THE WITNESS: Because of the small
22 numbers, that's correct, yes.
23 BY ATTORNEY DAVIES:
24 Q. With regard to the entire patient
25 population within the INCREASE study, was there a

1 statistically significant difference in
2 exacerbations of interstitial lung diseases on
3 treatment with inhaled trepostinil?
4 ATTORNEY DYKHUIS: Object to form.
5 THE WITNESS: I believe that there
6 was.
7 BY ATTORNEY DAVIES:
8 Q. Why do you believe there was an
9 effect seen in the larger patient population but
10 not in the subgroup of more mild PH patients with
11 respect to an effect on exacerbations in ILD?
12 ATTORNEY DYKHUIS: Objection.
13 Form.
14 THE WITNESS: It's purely because
15 of the numbers. We had, as I recall, 336
16 patients in the group as a whole, and
17 then those who had mild PH -- I don't
18 remember what the number was, it was 60
19 to 80 -- and once you have smaller
20 numbers, it becomes much more difficult
21 to hit statistical significance.
22 BY ATTORNEY DAVIES:
23 Q. Going back to your CV on page 29 --
24 and just let me know when you're back there --
25 there's an entry Number 24.

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1 Do you see that?
2 A. I do.
3 Q. And it refers to a derivation of a
4 simple risk calculator for predicting clinical
5 worsening in patients with pulmonary hypertension
6 due to interstitial lung disease.
7 Do you see that?
8 A. I do.
9 Q. And what does that paper describe,
10 generally?
11 A. That's the paper that I mentioned
12 earlier that's still in development, looking at all
13 the patients from an INCREASE study and looking at
14 their baseline characteristics to see if we can
15 identify a high-risk group versus a lower risk
16 group, a group of patients who are generally pretty
17 high risk.
18 Q. And what do you mean by "high risk"?
19 A. For having an event like mortality,
20 hospitalization, being events that are notable or
21 sometimes you put that in a compass endpoint of
22 clinical worsening. So that risk of having a bad
23 outcome or higher risk of having a bad outcome.
24 Q. Is that risk based on treatment with
25 inhaled treprostinil, or is that just they're high

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1 A. Not that springs to mind at the
2 moment.
3 Q. Have you received funding as
4 research grants from United Therapeutics?
5 A. Yes, I have.
6 Q. Do you have any sense for the amount
7 of money that you received in research grants from
8 United Therapeutics over the years?
9 ATTORNEY DYKHUIS: Object to form.
10 THE WITNESS: I don't have a good
11 sense.
12 BY ATTORNEY DAVIES:
13 Q. Is it more than \$100,000?
14 ATTORNEY DYKHUIS: Object to form.
15 THE WITNESS: I didn't get any
16 money from them for research. It goes to
17 my institution.
18 BY ATTORNEY DAVIES:
19 Q. Do you personally receive any other
20 grants from United Therapeutics which aren't for
21 research purposes?
22 ATTORNEY DYKHUIS: Object to form.
23 THE WITNESS: No.
24 BY ATTORNEY DAVIES:
25 Q. Can you turn to page 44 of your CV.

1 risk due to their disease generally?
2 ATTORNEY DYKHUIS: Object to form.
3 THE WITNESS: High risk due to
4 their disease generally. I believe the
5 way we're doing it is we're just looking
6 at the placebo arm to rule out the effect
7 of inhaled treprostinil on their own
8 interests.
9 BY ATTORNEY DAVIES:
10 Q. Other than your work in this case,
11 are you consulting with United Therapeutics in any
12 other matter?
13 A. I do consult with them in other
14 matters, you know, depending on what's going on.
15 You know, they have a working group, for example,
16 that talks about PH-ILD, and I'm part of that
17 working group. I'm on their speakers bureau.
18 So are there other ways in which I
19 collaborate with United Therapeutics.
20 Q. Other than being on the working
21 group with PH-ILD and the speakers group, how else
22 do you collaborate with United Therapeutics?
23 A. I'm the chair of the steering
24 committee for the Teton study.
25 Q. Anything else?

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1 A. (Witness complies with request.)
2 Q. This is in a section -- I'm sorry.
3 Are you there, Doctor?
4 A. I am there, yes.
5 Q. Okay. And if you flip over a page
6 or two, this is in a section of your CV titled
7 "Research Grants, Pharmaceutical Multicenter
8 Studies."
9 Do you see that?
10 A. Yes.
11 Q. Can you look at entry Number 31 on
12 page 44.
13 A. (Witness complies with request.)
14 Q. Are you there?
15 A. Yeah.
16 Q. What was your involvement in the
17 protocol for the LTI-301 study?
18 ATTORNEY DYKHUIS: Object to form.
19 THE WITNESS: I wasn't involved in
20 this protocol development. As I recall,
21 we were asked to be a center, and Moreau
22 [phon.] was the subinvestigator. I
23 wasn't even the principal investigator on
24 that.
25

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BY ATTORNEY DAVIES:

Q. What was your role as a subinvestigator in the study?

A. The fact that I was a subinvestigator just enabled me to see patients when they come in for study limits. Nothing more than that in terms of data analysis or anything else.

Q. Are you familiar with -- well, as your role as a subinvestigator and seeing patients as they came in, you've seen the dry powder inhaler that's used for administration of Yutrepia; correct?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: I haven't seen the Yutrepia device.

BY ATTORNEY DAVIES:

Q. Do you know what the Yutrepia device is?

A. I don't have a good idea what the device is.

Q. You do not?

A. I do not. I might have seen a picture of it, but I've never held one in my hands, no.

Q. Were you familiar with a Plastiapne inhaler, that's RS00 Model 8?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: I don't believe I am.

BY ATTORNEY DAVIES:

Q. Okay. So when patients came in as part of the LTI-301 study, what was your role as a subinvestigator when those patients came in?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: To be honest, I don't even remember seeing any of these patients. I might have been a sub-I on the protocol that we submitted without ever having seen one of these patients.

BY ATTORNEY DAVIES:

Q. When is the first time that you can recall hearing about Yutrepia or LIQ-861?

A. It's actually interesting, if I may. When you pointed me to this, I wasn't even aware that this was Liquidia's product. That's how much I recall about this study. I was very peripheral, and I've never saw any of these patients, and I never saw the device.

I was just listed as a sub-I at the start

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of the study, as were a bunch of our associates. The reason we do that is in case a PI is not available, someone can substitute for them and see a patient, but that never happened to me.

Q. Do you know who the PI was at your institution for this?

A. I believe it was Dr. Oxanna Slobin.

Q. We've been going for about an hour. Do you want take a break?

A. I'm good. We can carry on unless you need to take a break.

ATTORNEY DAVIES: I need to take a break, so if you don't mind, let's take a quick break.

THE VIDEOGRAPHER: We are off the record at 10:12.

(Recess taken from 10:12 a.m. to 10:21 a.m.)

THE VIDEOGRAPHER: We are on the record at 10:21.

BY ATTORNEY DAVIES:

Q. Welcome back, Doctor. Thank you for accommodating my request for a break, I appreciate that.

You mentioned earlier this morning an

initial protocol for the INCREASE study.

Do you recall that?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: We did talk about the INCREASE study and how it was formulated, yes.

BY ATTORNEY DAVIES:

Q. And I believe you testified that there had been a draft of a protocol that was provided from United Therapeutics, and you commented and had input on that; is that correct?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: That's correct.

BY ATTORNEY DAVIES:

Q. Do you know what the basis or rationale was for the INCREASE protocol draft from United Therapeutics?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: The premise was to give inhaled treprostinil and to see if it would be of benefit in patients with pulmonary hypertension associated with -- interstitial lung disease.

BY ATTORNEY DAVIES:

Q. Are you aware of whether it relied

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1 on any results from prior studies to support in the
2 design of the INCREASE protocol?
3 ATTORNEY DYKHUIS: Object to form.
4 THE WITNESS: I'm not aware of,
5 you know, the studies, I'm sure the
6 studies looked at all the studies in the
7 literature prior to that, but I don't
8 know of anyone that they leaned on.
9 BY ATTORNEY DAVIES:
10 Q. Can you go back to the beginning of
11 your declaration, which is Exhibit 2. And if you
12 go to the table of contents for your declaration,
13 just let me know when you're there.
14 A. (Witness complies with request.)
15 Yes.
16 Q. You mentioned that you drafted the
17 medical portions of your declaration. Can you
18 identify the portions of your declaration in the
19 table of contents that you prepared?
20 ATTORNEY DYKHUIS: Object to form.
21 I would say that I -- all portions I had
22 input on. I might have not been the
23 first draftee, but, you know, the
24 legalese stuff, there was the foundation
25 provided by counsel and, certainly if

1 there was anything that I didn't
2 understand it was explained to me. So it
3 was a lot of wordsmithing that went
4 around that.
5 But if we go through the medical
6 stuff, I know that -- I think it's just
7 about 58 points looks like it's more
8 legal stuff.
9 BY ATTORNEY DAVIES:
10 Q. When you said "points," Doctor,
11 you're referring to the first 58 paragraphs or more
12 of legal stuff that you didn't prepare?
13 ATTORNEY DYKHUIS: Object to form.
14 THE WITNESS: I wouldn't say I
15 didn't prepare it. I didn't prepare
16 necessarily the first draft, but then I
17 had input subsequently of the things that
18 I didn't understand; they were laid out
19 differently and I might have done some
20 wordsmithing myself amongst all the
21 different paragraphs. I don't recall
22 exactly what.
23 But if you look at from Scientific
24 Background, 59, 68, 69, 70, I believe
25 counsel helped put this table together.

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1 I think I provided the names of the
2 drugs, if I recall correctly.
3 Seventy-three, 74, this all looks
4 medical. Seventy-five, 76, 77, and then
5 all prior studies, I wrote that. I think
6 counsel was aware of some of these
7 studies and might have mentioned it, but
8 I really provided the verbiage that I
9 went through with each of these studies.
10 RISE IP, Sildenafil, pirfenidone, we
11 spoke about that.
12 The PERFECT study was mentioned.
13 I don't know if you wanted me to make my
14 way through the whole document and pick
15 out areas that I was involved in. The
16 INCREASE study, I believe that I was a
17 primary person who wrote that.
18 But then when you come to areas
19 like patent, you know, that's where
20 counsel helped to lay out the initial
21 foundation in terms of the first draft.
22 BY ATTORNEY DAVIES:
23 Q. There's reference on page 36 to the
24 prosecution history of the '327 patent.
25 A. Yeah.

1 Q. What is the prosecution history of
2 the '327 patent?
3 A. It's kind of a dying --
4 ATTORNEY DYKHUIS: Object to form.
5 Sorry, give me a moment to make any
6 objections.
7 THE WITNESS: I'm sorry.
8 ATTORNEY DYKHUIS: The other thing
9 I would say, Dr. Nathan, in this line of
10 questioning just a reminder I caution you
11 not to reveal of substance of any
12 communications with counsel, but you can
13 explain.
14 THE WITNESS: Thank you.
15 To my understanding, the
16 prosecution history is going backwards
17 and forwards between the courts in terms
18 of the lawsuit is brought and it's
19 revised and then the decision and then
20 you've got a counterclaim or whatever.
21 So that's how it's being prosecuted
22 historically.
23 BY ATTORNEY DAVIES:
24 Q. Do you recall reviewing the
25 prosecution history of the '327 patent in terms of

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<p>1 preparing your report?</p> <p>2 ATTORNEY DYKHUIS: Object to form.</p> <p>3 THE WITNESS: I did.</p> <p>4 BY ATTORNEY DAVIES:</p> <p>5 Q. You did.</p> <p>6 Can you go to page 43.</p> <p>7 A. (Witness complies with request.)</p> <p>8 Q. And there's a section of your report</p> <p>9 here entitled, "Liquidia will infringe the asserted</p> <p>10 claims of the '327 patent."</p> <p>11 Do you see that?</p> <p>12 A. I do.</p> <p>13 Q. Did you prepare this section of the</p> <p>14 report on the infringement of the claims of the</p> <p>15 '327 report, or is this legal opinion?</p> <p>16 ATTORNEY DYKHUIS: Object to form.</p> <p>17 THE WITNESS: It's my opinion.</p> <p>18 BY ATTORNEY DAVIES:</p> <p>19 Q. Did you prepare any portions of</p> <p>20 those, or did counsel prepare them?</p> <p>21 ATTORNEY DYKHUIS: Object to form.</p> <p>22 THE WITNESS: Honestly, I can't</p> <p>23 remember who contributed what to this</p> <p>24 first draft. It might well have been</p> <p>25 counsel because I wasn't familiar which</p>	<p>1 claims were being contested, but I</p> <p>2 certainly had input into this.</p> <p>3 BY ATTORNEY DAVIES:</p> <p>4 Q. We talked a little bit about</p> <p>5 statistical significance in a couple of different</p> <p>6 context earlier this morning.</p> <p>7 Do you recall that?</p> <p>8 A. Yes.</p> <p>9 Q. Is it possible to determine whether</p> <p>10 there has been a statistically significant</p> <p>11 difference within a single patient with respect to</p> <p>12 a treatment?</p> <p>13 ATTORNEY DYKHUIS: Object to form.</p> <p>14 THE WITNESS: No.</p> <p>15 BY ATTORNEY DAVIES:</p> <p>16 Q. Why not?</p> <p>17 A. You need --</p> <p>18 ATTORNEY DYKHUIS: Sorry, object</p> <p>19 to form.</p> <p>20 THE WITNESS: You need a large</p> <p>21 study to determine the statistical</p> <p>22 significant. There's a lot of things</p> <p>23 that can happen by chance in an</p> <p>24 individual patient, which if under</p> <p>25 treatment may or may not be attributable</p>
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<p>1 to the treatment. So you can't determine</p> <p>2 statistical significance in a single</p> <p>3 patient.</p> <p>4 BY ATTORNEY DAVIES:</p> <p>5 Q. Just to make it clear, and I don't</p> <p>6 think you heard me correctly, but I believe your</p> <p>7 testimony was that you cannot determine whether</p> <p>8 there is a statistically significant difference in</p> <p>9 a patient with respect to a treatment; correct?</p> <p>10 A. Correct.</p> <p>11 ATTORNEY DYKHUIS: Object to form.</p> <p>12 Just while there's a pause again,</p> <p>13 Doctor, just give me a moment to get in</p> <p>14 any objections.</p> <p>15 THE WITNESS: Yes.</p> <p>16 BY ATTORNEY DAVIES:</p> <p>17 Q. We've talked about pulmonary</p> <p>18 hypertension. What in your -- what in your words</p> <p>19 is pulmonary hypertension, Doctor?</p> <p>20 A. Pulmonary hypertension is a build-up</p> <p>21 of pressure in the pulmonary arterial circulation.</p> <p>22 Q. And how do you diagnose a patient</p> <p>23 with pulmonary hypertension in your practice?</p> <p>24 ATTORNEY DYKHUIS: Object to form.</p> <p>25 THE WITNESS: The diagnosis always</p>	<p>1 relies on a right heart catheterization</p> <p>2 to analyze the pressures.</p> <p>3 BY ATTORNEY DAVIES:</p> <p>4 Q. And what pressures from that right</p> <p>5 heart catheterization would indicate to you as a</p> <p>6 clinician there is pulmonary hypertension present?</p> <p>7 ATTORNEY DYKHUIS: Object to form.</p> <p>8 THE WITNESS: It depends which</p> <p>9 definition you're talking about, because</p> <p>10 there have been a lot of changes to the</p> <p>11 definition.</p> <p>12 When the INCREASE study was</p> <p>13 undertaken, we used what is known, an</p> <p>14 older definition of a mean pulmonary</p> <p>15 artery pressure of 25 milliliters or more</p> <p>16 accompanied by pulmonary vascular</p> <p>17 resistance of three or more wood units.</p> <p>18 That definition was subsequently</p> <p>19 changed at the Sixth World Symposium in</p> <p>20 2018, and the mean pulmonary artery</p> <p>21 pressure was lowered to greater than 20</p> <p>22 milliliters of mercury with the pulmonary</p> <p>23 vascular resistance remaining the same at</p> <p>24 three or more wood units.</p> <p>25 More recently, the European</p>

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<p>1 Society of Cardiology and the European 2 Respiratory Society came up with another 3 new division -- sorry, definition, where 4 they kept the mean pulmonary artery 5 pressure the same, greater than 6 20 milliliters of mercury but decided to 7 take the pulmonary vascular resistance 8 halfway down to two. 9 So based on the ESCERS guidelines 10 from 2022, the current definition is a 11 mean pulmonary artery pressure of 20 or 12 more milliliters of mercury accompanied 13 by a pulmonary vascular resistance of 14 greater than two wood units. 15 BY ATTORNEY DAVIES: 16 Q. And what was the definition that you 17 would have applied as of April 2020 with respect to 18 pulmonary hypertension? 19 ATTORNEY DYKHUIS: Object to form. 20 THE WITNESS: In 2020, we had the 21 definition from the World Symposium in 22 2018. But 2020 was the time that the 23 INCREASE study results came out, which 24 was formulated under the guise of the old 25 definition.</p>	<p>1 So what I would regard as 2 hypertension -- let me back up a little 3 bit. 4 Pulmonary hypertension is defined 5 by a mean pulmonary artery pressure of 6 greater than 20 milliliters of mercury. 7 You're talking about precapillary 8 pulmonary hypertension, then you need the 9 pulmonary vascular resistance component 10 of it. 11 So in 2020 what I would regard as 12 pulmonary hypertension would be a mean 13 pulmonary artery pressure of 20 or more 14 milliliters of mercury. 15 However, with regards to putting 16 patients on inhaled treprostinil, we have 17 to revert to the old definition because 18 we only know that the drug works in that 19 population of patients in the study. 20 BY ATTORNEY DAVIES: 21 Q. So you're saying the INCREASE study 22 applied a different definition of PH, which is more 23 narrow than the definition that existed in 2020; is 24 that correct? 25 ATTORNEY DYKHUIS: Object to the</p>
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<p>1 form. 2 THE WITNESS: That's true. It's 3 not by designed. The INCREASE study was 4 implemented and undertaken when we were 5 all functioning under the guise of the 6 old definition. 7 BY ATTORNEY DAVIES: 8 Q. We had talked earlier about the 9 groups of patients within pulmonary hypertension. 10 Do you recall that? 11 A. Yes. 12 Q. Which group do PH-ILD patients fall 13 into? 14 A. That would be Group 3. 15 Q. You also mentioned precapillary PH. 16 Which groups out of the five are precapillary, in 17 your opinion? 18 A. Group 1, Group 1, Group 3, Group 4, 19 and Group 5. 20 Q. And with respect to these groups, do 21 you view them as strict delineations, or do you 22 have patients that may have a mix of different 23 groups in your practice and experience? 24 ATTORNEY DYKHUIS: Object to form. 25 THE WITNESS: Most commonly it is</p>	<p>1 a mix. 2 BY ATTORNEY DAVIES: 3 Q. Can you explain that? What do you 4 mean by "Most commonly it is a mix"? What does 5 that mean? 6 A. The patients we see don't behave in 7 strict categories and frequently have comorbidities 8 where they have some lung disease and pulmonary 9 hypertension. Some heart disease and pulmonary 10 hypertension overlaid with chronic thromboembolic 11 pulmonary hypertension. 12 I said half jokingly that my favorite group 13 of pulmonary hypertension is group 10 where you 14 have some one, some two, some three, and some four, 15 because some patients are never quite that keen. 16 These categories are man-made, and we kind 17 of box ourselves into a corner by trying to put 18 patients in distinct categories, and the patients 19 don't always behave the way we would like it to be, 20 so they tend to cross over. 21 Q. So it would be common to see a 22 crossover, for example, of a patient who shows 23 signs of PAH, Group 1 might also shows signs of 24 Group 3 PH-ILD. Is that fair? 25 ATTORNEY DYKHUIS: Object to form.</p>

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1 THE WITNESS: That's a common
2 debate when it's a Group 1 with a little
3 bit of lung disease and when it's a
4 Group 3.
5 BY ATTORNEY DAVIES:
6 Q. So you would agree that in your
7 practice you do see patients who are a mix of both
8 Group 1 and Group 3; correct?
9 ATTORNEY DYKHUIS: Object to form.
10 THE WITNESS: It's very difficult
11 to sort out well, you know, this
12 percentage from Group 1 and this percent
13 is from Group 3.
14 The question becomes how much lung
15 disease is permissible in order to call
16 it Group 1 versus Group 3. And it's a
17 spectrum. And some people can look at
18 the same case and say, Well, I think this
19 is more Group 1, and other people might
20 look at the same case and say, No, I
21 think this is more Group 3.
22 When we look and try to make that
23 delineation, we look at how severe the
24 human dynamic impairment is, how severe
25 the lung impairment is based on lung

1 function tests, and we look at the CAT
2 scan to see how much lung scarring there
3 is in terms of making that determination.
4 BY ATTORNEY DAVIES:
5 Q. In your experience, what percent
6 of -- strike that.
7 So in your clinical experience, what
8 percent of the PH patients with treatment you've
9 overseen or been involved in have been a mix of
10 more than one of the groups of PH?
11 ATTORNEY DYKHUIS: Object to form.
12 THE WITNESS: That's a hard number
13 through the years to come up with. You
14 know, I would say maybe one-third could
15 have a compound into something else going
16 on, but that's not something I actively
17 collect to show.
18 BY ATTORNEY DAVIES:
19 Q. We've talked a lot about
20 interstitial lung disease. What is interstitial
21 lung disease, in your words?
22 ATTORNEY DYKHUIS: Object to form.
23 THE WITNESS: The interstitium of
24 the lung refers to the lattice lock
25 network within the lung parenchymal which

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1 surrounds the alveola or intersects. The
2 interstitium of the lungs.
3 When there's infiltration of the
4 interstitium usually in a diffuse matter
5 by scarring or fibrosis and/or
6 inflammation, the results are manifested
7 in interstitial lung disease.
8 BY ATTORNEY DAVIES:
9 Q. And have there been other words that
10 are used to describe interstitial lung disease in
11 the literature?
12 ATTORNEY DYKHUIS: Object to form.
13 THE WITNESS: The wording can be
14 confusing.
15 BY ATTORNEY DAVIES:
16 Q. I agree.
17 A. Pulmonary fibrosis, it refers to
18 lung scarring, and most of the patients with
19 interstitial lung disease of note, especially those
20 who have superimposed pulmonary hypertension, will
21 have pulmonary fibrosis.
22 And then even within the endopulmonary
23 fibrosis, if you open any textbooks, there are
24 probably over 200 courses of pulmonary fibrosis.
25 And so, one of the jobs we have when you see a

1 patient with ILD is to try to figure out what kind
2 of ILD they have.
3 Q. When did you first begin treating
4 pulmonary hypertension patients?
5 A. I remember seeing my first patient
6 with primary pulmonary hypertension, which is what
7 I used to call it when I was a resident in New York
8 in the late eighties.
9 Q. What is primary pulmonary
10 hypertension?
11 A. We changed the nomenclature. It's
12 now idiopathic pulmonary arterial hypertension. It
13 was changed in about 1996, if I recall. When I was
14 a fellow at Cedar Sinai Medical Center, we were one
15 of the few centers in the country to do the study
16 of REE treprostinil.
17 So as a person who enrolled in the study as
18 a fellow in 1988, and so you can say the late
19 eighties was the first time I started treating.
20 Although at that time we didn't know if the
21 medication worked or not. But then REE
22 treprostinil got approved in 1994, and then I was
23 treating off of it.
24 Q. What was the first time you recall
25 treating an ILD patient?

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<p>1 ATTORNEY DYKHUIS: Object to form.</p> <p>2 Q. I'll rephrase it.</p> <p>3 When was the first time you can recall</p> <p>4 treating a patient with ILD, interstitial lung</p> <p>5 disease?</p> <p>6 A. I actually do remember the patient I</p> <p>7 had with ILD, idiopathic pulmonary fibrosis, and</p> <p>8 that was in 1982 when I was an intern back in South</p> <p>9 Africa. I didn't treat her, because we had no</p> <p>10 treatment. But that was the first time I saw a</p> <p>11 patient with interstitial lung diseases.</p> <p>12 Q. Did that patient have -- also have</p> <p>13 pulmonary hypertension, or were they just -- not</p> <p>14 just, but did they solely have interstitial lung</p> <p>15 disease?</p> <p>16 A. At that point, I don't think we were</p> <p>17 even aware of pulmonary hypertension complicating</p> <p>18 interstitial lung disease. We're talking 1982.</p> <p>19 Q. Do you recall roughly when there was</p> <p>20 a recognition in the art of pulmonary hypertension</p> <p>21 complicating interstitial lung disease?</p> <p>22 ATTORNEY DYKHUIS: Object to form.</p> <p>23 THE WITNESS: If you go back to</p> <p>24 the literature, there are some papers</p> <p>25 from the 1980s describing pulmonary</p>	<p>1 hypertension complicating interstitial</p> <p>2 lung disease. It was only in the early</p> <p>3 2000s that more literature began to</p> <p>4 emerge about this.</p> <p>5 BY ATTORNEY DAVIES:</p> <p>6 Q. You mentioned, I believe, a couple</p> <p>7 different kinds of PH-ILD. Is that correct?</p> <p>8 A. I didn't.</p> <p>9 Q. You didn't? Is there only one type</p> <p>10 of PH-ILD, in your mind?</p> <p>11 A. Yeah. You have different kinds of</p> <p>12 ILDs. When you talk about PH-ILD as a group, and</p> <p>13 there's just one kind. It hasn't been segmented</p> <p>14 out. There might be some people who talk about</p> <p>15 severe pulmonary hypertension, and that came out</p> <p>16 from the European guidelines. But in my mind, it's</p> <p>17 all one big basket.</p> <p>18 Q. With respect to the differences in</p> <p>19 the underlying ILD, in your opinion did the</p> <p>20 INCREASE study evaluate PH-ILD patients who had all</p> <p>21 the different kinds of underlying ILD, or were</p> <p>22 there some groups that were excluded?</p> <p>23 ATTORNEY DYKHUIS: Object to form.</p> <p>24 THE WITNESS: We included many</p> <p>25 different forms of PH-ILD. Connective</p>
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<p>1 tissue disease, the effect of</p> <p>2 interstitial pneumonias with IPF</p> <p>3 being the major subgroup. Chronic</p> <p>4 hypersensitivity being another one.</p> <p>5 CPFE, combined chronic fibrosis with</p> <p>6 emphysema being another one.</p> <p>7 There are other courses, as I</p> <p>8 mentioned. Some of those are broad</p> <p>9 categories. I don't recall if we had</p> <p>10 occupational lung disease in there or</p> <p>11 not. If we did, it might have been one</p> <p>12 or two patients at the most.</p> <p>13 BY ATTORNEY DAVIES:</p> <p>14 Q. Any other types of ILD that were not</p> <p>15 covered by the patient population in the INCREASE</p> <p>16 study?</p> <p>17 ATTORNEY DYKHUIS: Objection to</p> <p>18 form.</p> <p>19 THE WITNESS: What I would say is</p> <p>20 just numerically, probably 95 to</p> <p>21 99 percent of the disease categories were</p> <p>22 covered by the INCREASE study.</p> <p>23 So let me qualify that. I said in</p> <p>24 terms of causes, some of them are</p> <p>25 extremely rare. The most common ones and</p>	<p>1 what I'm trying to articulate is that of</p> <p>2 the universe of patients with</p> <p>3 interstitial lung disease, fibrotic</p> <p>4 interstitial lung disease, we probably</p> <p>5 covered the bases for 95 to 99 percent.</p> <p>6 And that's a rough guesstimate on my</p> <p>7 part.</p> <p>8 BY ATTORNEY DAVIES:</p> <p>9 Q. When was the first time that you</p> <p>10 recall prescribing treprostinil to a patient?</p> <p>11 A. When it first became available</p> <p>12 subcutaneously, and I believe it was in 2002 or</p> <p>13 thereabouts.</p> <p>14 Q. Do you recall what you used that to</p> <p>15 treat in 2022?</p> <p>16 ATTORNEY DYKHUIS: Object to form.</p> <p>17 THE WITNESS: Some form of</p> <p>18 pulmonary arterial hypertension.</p> <p>19 BY ATTORNEY DAVIES:</p> <p>20 Q. And when is the first time you can</p> <p>21 recall using inhaled treprostinil in a patient?</p> <p>22 A. I think it was approved around 2010,</p> <p>23 I believe. At least that's when the paper came</p> <p>24 out. So soon thereafter, I believe.</p> <p>25 Q. When was the first time that you</p>

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1 used inhaled treprostinil to treat PH-ILD?
2 ATTORNEY DYKHUIS: Object to form.
3 THE WITNESS: I don't recall that.
4 What I would say -- and this goes back to
5 that spectrum of Group 1 versus
6 Group 3 -- there are patients who have
7 lung disease whose hemodynamics are
8 severe enough out of proportion, so to
9 speak, from the lung disease that I would
10 regard them as having Group 1 pulmonary
11 arterial hypertension even in the context
12 of having interstitial lung disease.
13 So under that guise, I would treat
14 patients with PAH who had lung disease.
15 BY ATTORNEY DAVIES:
16 Q. When was the first time that you can
17 recall treating a patient who had PAH with
18 underlying interstitial lung disease with inhaled
19 treprostinil?
20 ATTORNEY DYKHUIS: Objection to
21 form.
22 THE WITNESS: I don't recall that.
23 BY ATTORNEY DAVIES:
24 Q. Was it before the INCREASE study?
25 ATTORNEY DYKHUIS: Objection to

1 form.
2 THE WITNESS: Yes.
3 BY ATTORNEY DAVIES:
4 Q. Okay. Was it soon after inhaled
5 treprostinil's approval around 2009?
6 ATTORNEY DYKHUIS: Object to form.
7 THE WITNESS: I don't think so. I
8 doubt it. I don't recall specifically.
9 BY ATTORNEY DAVIES:
10 Q. Why did you choose to use inhaled
11 treprostinil to treat patients with PAH and
12 underlying ILD?
13 ATTORNEY DYKHUIS: Object to form.
14 THE WITNESS: We had the INCREASE
15 study results, and I knew about them
16 before the drug was approved.
17 BY ATTORNEY DAVIES:
18 Q. But you used inhaled treprostinil in
19 PAH patients with underlying IDL before 2016,
20 didn't you?
21 ATTORNEY DYKHUIS: Objection to
22 form.
23 THE WITNESS: You know, going back
24 many years, I don't remember a distinct
25 case, to be quite honest.

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1 Just by virtue of the patient
2 volumes I see with PH, with interstitial
3 lung disease, I'm assuming that I
4 probably did, but I don't know for sure.
5 Any time distinctly that I remember using
6 it was after the INCREASE study results
7 were known and off-label at that time
8 because the drug wasn't approved as yet.
9 BY ATTORNEY DAVIES:
10 Q. You were aware that others were
11 using inhaled treprostinil to treat patients with
12 PAH and underlying ILD before recruitment for the
13 INCREASE study, though; correct?
14 ATTORNEY DYKHUIS: Object to form.
15 THE WITNESS: Based on some of the
16 papers in the literature, it does appear
17 so, yes.
18 BY ATTORNEY DAVIES:
19 Q. So why were you personally
20 comfortable prescribing inhaled treprostinil to
21 these PAH patients with underlying ILD?
22 ATTORNEY DYKHUIS: Objection to
23 form.
24 THE WITNESS: As I said, any time
25 I remember distinctly was after INCREASE

1 became available. Patients -- prior to
2 that I would treat patients with some
3 interstitial lung disease if their
4 pulmonary hypertension was
5 disproportionate and I regarded them as
6 having more of a Group 1 phenotype.
7 Typically at that point inhaled
8 treprostinil wasn't my go-to drug. The
9 easiest drug to get was Sildenafil, which
10 is generally what I used if I was going
11 to treat patients who had any form of
12 lung disease and associated pulmonary
13 hypertension.
14 BY ATTORNEY DAVIES:
15 Q. So even though you can't recall a
16 particular time, you do agree that you used inhaled
17 treprostinil to treat PH patients whose PH was
18 disproportionate to their underlying ILD before the
19 INCREASE study; right?
20 ATTORNEY DYKHUIS: Object to form.
21 THE WITNESS: I probably did.
22 We're going back many years now. If you
23 look at one group of patients, and that's
24 connective tissue disease patients like
25 scleroderma who form at least about

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1 30 percent of the Group 1 PH patients, if
2 you look at the CAT scans, it's very
3 unusual for them not to have some lung
4 disease.

5 And so even if the clinical trials
6 of Group 1 PH, there were likely a bunch
7 of connective tissue disease patients who
8 had some lung disease that we just didn't
9 know about.

10 BY ATTORNEY DAVIES:

11 Q. So I believe you said even in the
12 clinical trials of inhaled trepostinil for Group 1
13 PAH, there were likely some patients with
14 underlying ILD as part of that study as well?

15 ATTORNEY DYKHUIS: Object to form.

16 THE WITNESS: I'm speculating.
17 What we -- for all the clinical trials in
18 Group 1 PAH, what we used as the cut
19 point to get into the study was the
20 forced vital capacity.

21 If the forced vital capacity was
22 greater than about 70 percent, then the
23 patient goes into the study. Can we rule
24 out that a patient with the FVC of
25 72 percent didn't have a little bit of

1 lung disease, no, we can't, but we don't
2 know.

3 So I'm speculating that maybe
4 there was some patients who were included
5 in the study, but these were patients who
6 were defined as Group 1 PAH based on our
7 criteria at the time.

8 BY ATTORNEY DAVIES:

9 Q. I believe you said it was likely
10 that such patients would have been in those
11 studies; correct?

12 ATTORNEY DYKHUIS: Object to form.

13 THE WITNESS: It's possible, and
14 it's speculative on my part, because I
15 don't know.

16 BY ATTORNEY DAVIES:

17 Q. When was the first time that you can
18 recall treating a PH-ILD patient with inhaled
19 trepostinil?

20 A. After the INCREASE study results
21 came out. That's when I first can recall treating
22 a patient with PH-ILD with inhaled trepostinil.

23 But it was a patient, once again, who had
24 more of the Group 1 phenotype with more moderate to
25 severe pulmonary hypertension.

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1 Q. And when did the results come out
2 for INCREASE?

3 ATTORNEY DYKHUIS: Object to form.

4 THE WITNESS: I was first made
5 aware of the results ruts, as I said
6 earlier when you asked me earlier towards
7 the end of February 2020. There was a
8 press release from the company around
9 that time just providing the top line
10 results, and then there was a publication
11 in the New England June Journal of
12 Medicine which I think was around January
13 of 2021.

14 BY ATTORNEY DAVIES:

15 Q. And when was the first time that you
16 recall treating a PH-ILD patient with Sildenafil?

17 ATTORNEY DYKHUIS: Object to form.

18 THE WITNESS: I don't recall
19 exactly, you know, going back 15 years,
20 maybe more.

21 BY ATTORNEY DAVIES:

22 Q. So at least 15 years ago?

23 A. It could have been less than that.
24 I don't know.

25 Q. But it would have -- you would have

1 treated a patient, a PH-ILD patient with Sildenafil
2 before receiving the results of the INCREASE study;
3 correct?

4 ATTORNEY DYKHUIS: Object to form.

5 THE WITNESS: Let me qualify that.
6 These are patients who had more of a PAH
7 phenotype in the context of some
8 underlying interstitial lung disease. So
9 I wouldn't regard them as PH-ILD. I
10 would regard them as having some lung
11 disease but more of a Group 1 PAH
12 phenotype.

13 BY ATTORNEY DAVIES:

14 Q. When was the first time under your
15 definition of PH-ILD you can recall treating a
16 patient with Sildenafil?

17 ATTORNEY DYKHUIS: Object to form.

18 THE WITNESS: PH-ILD, if you go by
19 the new definition versus the old
20 definition, MPAP, mean pulmonary artery
21 pressure greater than 20, greater than
22 25. It's a spectrum. And only if they
23 were on the more severe end of the
24 spectrum would I treat them.

25 So when you say PH-ILD, it was

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1 around that time, but it was the much
2 more severe patients who had more of the
3 Group 1 PAH phenotype.
4 BY ATTORNEY DAVIES:
5 Q. You said it was around that time.
6 What time are you referring to? About 15 years
7 ago?
8 A. About 15 years ago.
9 Q. When is the first time that you
10 recall using Iloprost to treat PH-ILD?
11 ATTORNEY DYKHUIS: Object to form.
12 THE WITNESS: We were part of the
13 a study that's called Active Study
14 looking at Iloprost to treat pulmonary
15 hypertension associated with IPF.
16 So it was a specific IPF
17 subpopulation of ILD, and it was a
18 negative study. And I don't recall ever
19 using inhaled Iloprost for pulmonary
20 hypertension with interstitial lung
21 disease.
22 BY ATTORNEY DAVIES:
23 Q. You mentioned the phrase earlier
24 that in some of these patients their pulmonary
25 hypertension is out of proportion to their

1 underlying ILD.
2 Do you recall saying that?
3 A. I do.
4 Q. And when you write prescriptions
5 that would have been off-label at the time for
6 PH-ILD patients, is that the language that you use
7 on those prescriptions when you prescribe inhaled
8 treprostinil?
9 ATTORNEY DYKHUIS: Object to form.
10 THE WITNESS: As I said, I don't
11 recall prescribing it. I withdraw that.
12 I thought you said, I heard inhaled
13 Iloprost. Inhaled treprostinil.
14 The language I would use
15 post-INCREASE was that this patient gets
16 to have interstitial lung disease, but
17 clearly the pulmonary hypertension is out
18 of proportion to the extent of the
19 underlying interstitial lung disease;
20 therefore I believe they have a Group 1
21 phenotype.
22 BY ATTORNEY DAVIES:
23 Q. Did you use that language and
24 descriptions for inhaled treprostinil prior to
25 results of the INCREASE study?

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1 ATTORNEY DYKHUIS: Object to form.
2 THE WITNESS: I don't recall doing
3 that.
4 BY ATTORNEY DAVIES:
5 Q. You never recall doing that?
6 A. As I mentioned, my go-to medication
7 at that time just because it was cheaper to get a
8 hold of and easier was Sildenafil. Can I attest to
9 that a hundred percent? I can't remember every
10 prescription I wrote. But that wasn't my standard
11 practice by far.
12 Q. So sitting here today, you have no
13 recollection of ever prescribing inhaled
14 treprostinil in a PH-ILD patient prior to receiving
15 notice of the results of the INCREASE study; is
16 that correct?
17 A. Not to my recollection, but once
18 again, I can't remember every prescription I've
19 written.
20 Q. And even though you don't have a
21 specific recollection, you would agree that
22 probably did happen prior to you receiving the
23 results of the INCREASE study?
24 ATTORNEY DYKHUIS: Object to form.
25 THE WITNESS: I don't recall it

1 happening.
2 BY ATTORNEY DAVIES:
3 Q. Okay. Do you believe it did happen
4 nonetheless?
5 ATTORNEY DYKHUIS: Object to the
6 form.
7 THE WITNESS: I don't recall it
8 happening.
9 BY ATTORNEY DAVIES:
10 Q. And I'm not asking whether or not
11 you recall or not. I'm saying do you believe that
12 it happened based on the number of patients that
13 you saw, based on the lack of clear delineations
14 between the groups of PH?
15 ATTORNEY DYKHUIS: Objection to
16 form.
17 THE WITNESS: I don't think it
18 happened, because I don't believe it
19 happened, but I cannot attest to it a
20 hundred percent, having written thousands
21 of prescriptions over the years. I don't
22 know.
23 BY ATTORNEY DAVIES:
24 Q. You mentioned -- you mentioned using
25 Sildenafil for treatment of PH-ILD; correct?

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<p>1 ATTORNEY DYKHUIS: Object to form.</p> <p>2 THE WITNESS: For patients who had</p> <p>3 some ILD and associated pulmonary</p> <p>4 hypertension that appeared more severe</p> <p>5 than the extent of the underlying lung</p> <p>6 disease. I do want to make that</p> <p>7 distinction rather than the broad blanket</p> <p>8 term of PH-ILD, which can be any PH in</p> <p>9 the context of ILD.</p> <p>10 BY ATTORNEY DAVIES:</p> <p>11 Q. And with regard to those patients,</p> <p>12 in your opinion their PH-ILD was treated; correct?</p> <p>13 ATTORNEY DYKHUIS: Object to form.</p> <p>14 THE WITNESS: Are you referring to</p> <p>15 the PH component or the ILD component?</p> <p>16 BY ATTORNEY DAVIES:</p> <p>17 Q. Well, let me -- is there a</p> <p>18 distinction in your mind?</p> <p>19 A. Yeah, we treat the ILD and we'll</p> <p>20 treat the PH. PH-ILD is really two diseases</p> <p>21 together.</p> <p>22 Q. So if I have a PH-ILD patient and I</p> <p>23 treat the PH component in that patient, do you</p> <p>24 consider that treatment of PH-ILD or not?</p> <p>25 ATTORNEY DYKHUIS: Object to form.</p>	<p>1 THE WITNESS: Are you talking</p> <p>2 about currently or prior to the INCREASE</p> <p>3 study?</p> <p>4 BY ATTORNEY DAVIES:</p> <p>5 Q. Let's start with prior to the</p> <p>6 INCREASE study.</p> <p>7 A. Yes. I considered treating PH-ILD</p> <p>8 in that context, but once again, I feel like I have</p> <p>9 to qualify it every time you mention PH-ILD prior</p> <p>10 to the INCREASE study as patients who had pulmonary</p> <p>11 hypertension that appeared to be out of proportion</p> <p>12 to their interstitial lung disease.</p> <p>13 Q. When you say prior to the INCREASE,</p> <p>14 you're talking about the prior to initiation of</p> <p>15 that study or some other time point?</p> <p>16 A. Prior to the results coming out of</p> <p>17 the meeting where there were results.</p> <p>18 Q. So prior to you being aware of the</p> <p>19 results from the INCREASE study, if you prescribed</p> <p>20 a medication to a patient with PH-ILD, did you</p> <p>21 consider -- let me start this whole thing over.</p> <p>22 Prior to you hearing the results of the</p> <p>23 INCREASE study, did you consider yourself to have</p> <p>24 treated PH-ILD in a patient if you just impacted</p> <p>25 the PH component of the disease?</p>
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<p>1 ATTORNEY DYKHUIS: Objection to</p> <p>2 form.</p> <p>3 THE WITNESS: I didn't know if I</p> <p>4 was treating it. I was hoping I was</p> <p>5 treating it. I'd like to make the</p> <p>6 distinction of treating PH versus helping</p> <p>7 the patient, because we know that these</p> <p>8 drugs, Sildenafil, inhaled treprostinil,</p> <p>9 they lower the pressures in the lung.</p> <p>10 That's treating the pulmonary</p> <p>11 hypertension.</p> <p>12 What I didn't know is if treating</p> <p>13 and lowering the pressures potentially</p> <p>14 would result or manifest as a clinical</p> <p>15 benefit.</p> <p>16 BY ATTORNEY DAVIES:</p> <p>17 Q. And what in your mind was a clinical</p> <p>18 benefit?</p> <p>19 A. There could be multiple</p> <p>20 manifestations of the clinical benefit. If the</p> <p>21 patient comes back and says, Gosh, I feel better,</p> <p>22 that's benefit. If they come back and their</p> <p>23 six-minute walk distance has increased, they say I</p> <p>24 feel better, then that's a benefit.</p> <p>25 So in my mind, every patient who I've</p>	<p>1 treated like that was an end of point study. They</p> <p>2 told me how they were doing. If they felt better,</p> <p>3 great. If not, then frequently I would stop the</p> <p>4 medication.</p> <p>5 What I didn't know, even if they felt</p> <p>6 better, is whether or not it was an effect of the</p> <p>7 drug or not. Because you know that there could be</p> <p>8 a big placebo component even if you go to the</p> <p>9 INCREASE study. There were patients who were</p> <p>10 treated with inhaled treprostinil -- sorry, with</p> <p>11 placebo who had increases in their walk distance.</p> <p>12 The only way you can tell if the drug works or not</p> <p>13 are these big population-based studies like</p> <p>14 INCREASE, where you have a large group that gets</p> <p>15 drug and a large group that doesn't get drug.</p> <p>16 Q. So in an individual patient setting,</p> <p>17 how do you know if the treatments that you are</p> <p>18 giving to your patients are actually effective or</p> <p>19 not since it's not in a large group setting?</p> <p>20 ATTORNEY DYKHUIS: Objection to</p> <p>21 form.</p> <p>22 THE WITNESS: As long as a patient</p> <p>23 tells me they feel better, I don't really</p> <p>24 concern myself if it's a placebo effect</p> <p>25 or if it's real. If they feel better,</p>

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1 I'll do anything and continue any
2 medication that they perceive as making
3 them feel better.
4 BY ATTORNEY DAVIES:
5 Q. But in your mind, is treatment -- in
6 your mind, is the definition of treatment only
7 those instances where the drug has a demonstrated
8 impact on the patient?
9 ATTORNEY DYKHUIS: Objection to
10 form.
11 THE WITNESS: No, that's not my
12 definition of treatment.
13 BY ATTORNEY DAVIES:
14 Q. Okay. If there's a placebo
15 treatment, is that treatment?
16 ATTORNEY DYKHUIS: Objection to
17 form.
18 THE WITNESS: Yes. If the patient
19 feels better, you've done something via
20 placebo and it's resulted in improvement,
21 so I would regard that as treatment.
22 BY ATTORNEY DAVIES:
23 Q. Treprostinil is in part a
24 vasodilator; correct?
25 A. That's correct.

1 Q. What hemodynamics impacted by
2 treprostinil, in your mind, inform whether or not
3 there has been a treatment effect?
4 ATTORNEY DYKHUIS: Object to form.
5 THE WITNESS: If you go back to
6 the definition, if you lower the mean
7 pulmonary artery pressure and you lower
8 the pulmonary vascular resistance, then
9 the drug has acted as a vasodilator and
10 has been a treatment effect.
11 The key element is whether or not
12 that treatment effect translates to
13 clinical benefit for the patient. Let me
14 go back as an example to the RISE IP
15 study where we know clearly that
16 riociguat is a pretty potent vasodilator
17 and lowers the pressures, and yet
18 patients didn't benefit and in actual
19 fact they were harmed by them riociguat.
20 So A frequent effect on the
21 pulmonary hypertension doesn't equate
22 necessarily to clinical benefit for the
23 patient.
24 BY ATTORNEY DAVIES:
25 Q. Do you measure -- in your clinical

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1 practice, do you measure the hemodynamics of
2 patients on inhaled treprostinil as part of
3 monitoring those patients?
4 A. Typically, no. Once we start them
5 on treatment, unless an additional question arises,
6 it is an invasive test on riociguat and I ask a
7 specific question you need answered by the test,
8 then typically no.
9 Q. Which hemodynamic -- strike that.
10 Which improvements in which hemodynamic
11 parameters would, in your mind, be indicative of a
12 clinical improvement?
13 ATTORNEY DYKHUIS: Object to form.
14 THE WITNESS: None.
15 BY ATTORNEY DAVIES:
16 Q. None?
17 A. None.
18 Q. Is it your testimony that based on
19 hemodynamic data you cannot predict in any way the
20 clinical effects of treprostinil?
21 ATTORNEY DYKHUIS: Form.
22 THE WITNESS: Let me differentiate
23 Group 1 from Group 3.
24 BY ATTORNEY DAVIES:
25 Q. Okay.

1 A. Because Group 1, the hemodynamic
2 effect is a good surrogate for likely clinical
3 benefit. There probably have been instances, I
4 can't cite them and I'm sure there have been
5 instances of drugs that have had a hemodynamic
6 effect that haven't come to market because they
7 haven't manifested clinical benefit.
8 In Group 3 or PH-ILD, all bets are off,
9 because now you have the superimposed interstitial
10 lung disease, and so my definitive no was more
11 directed to PH-ILD.
12 What I'm saying is Group 1 is a good
13 surrogate, not always, but in Group 3 it's not
14 necessarily a surrogate for benefit.
15 Q. Why, in your mind, is it not
16 necessarily a surrogate for clinical benefit in
17 Group 3?
18 ATTORNEY DYKHUIS: Object to form.
19 THE WITNESS: Because you have the
20 added layer of the pulmonary parenchymal
21 interstitial lung disease. I'm happy to
22 do a deep dive into it if you like. Let
23 me do it so maybe you can -- because I'll
24 try to do it as best I can.
25

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BY ATTORNEY DAVIES:

Q. Go ahead.

A. If you have fibrosis of the lung, there are many things that contribute to the pulmonary hypertension. You have obliteration of the vessels, you have distortion of the vessels. There's a lot of different things going on in the lungs as opposed to Group 1 PAH where they typically have normal lung disease, let's say.

When -- let's say you have 50 percent of your pulmonary vasculature that's totally obliterated and unavailable for perfusion, then the right side of the heart has to put out the whole cardiac outputs into 50 percent of the vasculature.

So when you talk about the velocity of the blood flow, the sheer stretch involved, we don't know if that's harmful to the vasculature itself. And we don't know when you have distortion of the vasculature and you have these accelerated blood cells coming in how that impacts overall well-being of the patient.

Another concept to remember is take the same example where you have 50 percent of your blood flow -- say a hundred percent of your blood flow going to residual 50 percent of the vascular,

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difference with inhaled treprostinil is, number one, it's inhaled. So most of the drug is going to the best ventilated areas of the lung.

If the drug is going to the best ventilated areas of the lung and dilating the blood vessels in those best ventilated areas, then you get the blood redirected to the best ventilated areas.

That's would be just one example of how that might be different to the scenario you I gave you, which is more applicable, say, to a systemically administered agent. You also have more drug deposition within the area of the lung where you want it to go compared to a systemically administered drug where in the context of fibrotic lung disease you don't know where the drug is going.

So more local deposition and, you know -- but to your point, that's how I was skeptical that the INCREASE study would be positive. And -- but at the end of the day it was unequivocally positive with benefit in the primary secondary

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and let's say the velocity has to be processed fast to maintain your cardiac output.

Well, you also need gas exchange between the alveoli line and the blood flowing through it, and now you have fibrosis interlaced. Typically in a normal person when a red blood cell traverses the alveoli and the capillaries, it gets fully oxygenated one-third of the way through.

But now you have a situation of fibrosis and you have these accelerated red cell particles that are more accelerated because there's been vasodilation, an ability to fix gas exchange becomes impaired.

So that just one example -- two examples of how lung disease makes it very different in terms of lowering the pressures enabling more blood to go through, and there can be a negative downside to that.

Q. Why, in your opinion, see a treatment affect with inhaled treprostinil in PH-ILD patients in the INCREASE study?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: I think a difference, for example, we can apply riociquat to what I just said. A

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biomarker. And so thankfully it works and, you know, it's available to help the patients.

BY ATTORNEY DAVIES:

Q. You talk about VQ mismatch a number of times in your declaration.

Do you recall that?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: Yes.

BY ATTORNEY DAVIES:

Q. What is VQ mismatch?

A. I thought I explained it pretty well in my declaration. I'm not going to read it. I'm sure you've read it.

Q. If you can explain it.

A. It's easier for me just to read from my declaration.

Q. That's fine.

A. I'll explain. For gas exchange to take place, you need VQ matching. The air going into the lungs and into the alveola sac has to be accompanied by blood through the capillaries to interface with the air.

If you have areas of the lung where you have VQ mismatch, there are two extremes of that.

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1 You can have no air and blood flow; and we refer to
2 it as shunt. The area is being shunted to the
3 lungs without opportunity for gas exchange.
4 If you have areas of the lung, opposite end
5 of the spectrum where you just have air flow, no
6 blood flow because there's been fibrosis, the blood
7 vessels has been destroyed, then we could talk
8 about that as dead space ventilation. Air is going
9 in and going out and not participating in gas
10 exchange.
11 Between those two extremes of dead space
12 ventilation and shunt physiology, we have a
13 gradation in the spectrum once again and VQ
14 mismatch with the amount of ventilation going in
15 doesn't match up with the perfusion going by.
16 Q. So a concern with giving a, for
17 example, systemic oral vasodilator, maybe you
18 actually exacerbate that VQ mismatch by attempting
19 to have blood go to areas of the alveoli that can't
20 actively participate in oxygen exchange; correct?
21 ATTORNEY DYKHUIS: Object to form.
22 THE WITNESS: That is a theory of
23 concern.
24 BY ATTORNEY DAVIES:
25 Q. Okay. Do you believe that theory?

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1 THE WITNESS: We don't know, but
2 it could have been a contributing factor,
3 but we don't know.
4 BY ATTORNEY DAVIES:
5 Q. I think you said one of the
6 advantages of an inhaled therapy is that it
7 actually is preferentially directed to the healthy
8 portions of the lung and you avoid some of the
9 concerns associated with the VQ mismatch. Is that
10 correct?
11 ATTORNEY DYKHUIS: Object to form.
12 THE WITNESS: Theoretically
13 possible. Not healthy, relatively
14 healthier, and so -- but you've got the
15 general principle correct.
16 BY ATTORNEY DAVIES:
17 Q. In your opinion, is that part of the
18 reason why inhaled treprostinil showed a clinical
19 benefit in the INCREASE study?
20 ATTORNEY DYKHUIS: Objection to
21 form.
22 THE WITNESS: It's possible it
23 might have had a role, but we don't know.
24 BY ATTORNEY DAVIES:
25 Q. What is your opinion?

1 ATTORNEY DYKHUIS: Object to form.
2 THE WITNESS: It's possible that
3 it does happen. It's possible that it
4 happens in different lung units in the
5 same patient.
6 There have been studies around
7 this, I believe, for many years ago that
8 maybe a test of VQ mismatch being an
9 issue. I can't recall that study. I'm
10 speculating, there are probably studies
11 out there that demonstrated that.
12 So it's a theory, and it's
13 something we lean on sometimes when you
14 can't find a good explanation for
15 worsening oxygenation.
16 So, I think it probably does
17 happen in some patients, yes.
18 BY ATTORNEY DAVIES:
19 Q. In your opinion, was the fact that
20 riociquat was a systemic orally administered
21 vasodilator, do you believe that that was a reason
22 for why you had increased death in the study
23 population and the reason why that study failed?
24 ATTORNEY DYKHUIS: Objection to
25 form.

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1 ATTORNEY DYKHUIS: Objection to
2 form.
3 THE WITNESS: Why the study was
4 positive?
5 BY ATTORNEY DAVIES:
6 Q. Correct.
7 A. I don't know. I actually when I'm
8 giving talks I get asked this question all the
9 time. What is the reason, what's the biologic
10 reason, and I don't think anyone can say for sure
11 what the biologic reason is.
12 But what I say is we can make sure they
13 have a sound biologic reason of why a drug should
14 work but doesn't, or would you have some questions
15 about how it does work and not know exactly and yet
16 it has clinical benefits -- benefit. I would much
17 rather take the benefits to the patient than know
18 exactly how it works.
19 There are all these theories that, you
20 know, it goes to the best ventilated areas. Just
21 enough drug and the enough dose to provide benefit,
22 but we don't know for sure how or why it works.
23 You know, on a cellular level there are all
24 sorts of pathways to show positive benefits, and we
25 don't know which one might have been of benefit to

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1 the patients. So we can't pinpoint exactly how it
2 works, and it probably works by multiple different
3 ways in terms of providing benefit.

4 Q. We talked earlier about the fact
5 that Tyvaso was initially approved in Group 1 in
6 2009.

7 Do you recall that?

8 A. Yes.

9 Q. That was a nebulized formulation in
10 2009; is that correct?

11 A. Yes.

12 Q. So in 2009 with the approval of
13 Tyvaso inhaled, practitioners in the field would
14 have recognized that that treprostinil was going to
15 be preferentially delivered to the vaso ventilated
16 portions of the lung; correct?

17 ATTORNEY DYKHUIS: Object to form.

18 THE WITNESS: It was approved for
19 Group 1 PAH patients who generally don't
20 have lung disease, so you don't have this
21 VQ imbalance in Group 1 patients as you
22 do with patients with lung disease.

23 I just want to come back to the
24 question that you asked previously.

25 There might be people who say that

1 inhaled treprostinil works because it's a
2 vasodilator, it's clear it's a
3 vasodilator that you see in patients and
4 that's why it worked.

5 But in patients with lung disease,
6 we know it's not as simple as that we
7 have other drugs like riociguat, which
8 are also very good vasodilators and it
9 failed. So I think to say well, it's a
10 vasodilator, it's obvious that it worked.
11 It's kind of naive without taking into
12 account the prior literature.

13 BY ATTORNEY DAVIES:

14 Q. Isn't the difference in
15 administration between riociguat being systemically
16 administered -- let me start over.

17 The fact that riociguat is a systemic
18 vasodilator because it's given orally, it's a
19 differentiating factor as compared to inhaled
20 treprostinil; correct?

21 ATTORNEY DYKHUIS: Object to form.

22 THE WITNESS: It's one of many
23 differentiating factors.

24 BY ATTORNEY DAVIES:

25 Q. I want to go back to a question I

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1 asked you earlier.

2 So after receiving -- after you received
3 the first report of results from the INCREASE
4 study, did you believe that you were treating the
5 PH-ILD in a patient if you were just treating the,
6 or impacting the PH component?

7 ATTORNEY DYKHUIS: Object to form.

8 THE WITNESS: I want to make sure
9 I understood that correctly. Whenever I
10 treat a patient, I want to benefit the
11 patient.

12 So after the INCREASE study, I
13 believe that we were treating the patient
14 because they were having benefit.

15 BY ATTORNEY DAVIES:

16 Q. So your -- is it true that your
17 definition of treatment, both before and after the
18 INCREASE study, was that if you saw a benefit in
19 the patient, it didn't matter whether the effects
20 of the inhaled treprostinil were on PH or were on
21 the ILD component. Either way you consider that to
22 be treatment if there was an improvement in the
23 patient?

24 ATTORNEY DYKHUIS: Object to form.

25 THE WITNESS: Improvement in the

1 patient is very likely -- much more
2 likely related to the PH component.

3 When you treat the fibrosis
4 component and you've seen this with
5 anti-fibrotic drugs, all it does is delay
6 progression of the fibrosis. Once
7 scarring is there, you can't reverse it.
8 So my belief was that it was related
9 mostly to an impact on the pulmonary
10 hypertension.

11 BY ATTORNEY DAVIES:

12 Q. Okay. Do you believe that inhaled
13 treprostinil in the INCREASE study had any role on
14 reversing the pulmonary fibrosis in those patients?

15 A. That would be speculative. I mean,
16 there are mechanisms whereby it could have
17 anti-fibrotic properties, and that's the reason for
18 the Teton study to see if we can validate that.

19 What we saw, specifically in the subgroups
20 post hoc analysis or the numbers, is that it did
21 appear, the FVC was about the zero line, the line
22 of unity starting out at 16 weeks.

23 So it gives the appearance of apparent
24 improvement. But the error bars crossed the zero
25 line, and so there can be vacillations in the FVC.

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1 So we don't know. To say that there's an
2 improvement in the fibrosis is very speculative.
3 When you have fibrosis being laid down,
4 there are various stages of fibrosis from early
5 collagen deposition, fibroblast activation, early
6 scarring to end stage honeycombing.
7 Is it conceivable that anti-fibrotic drugs
8 can reverse the earlier stages of fibroblast
9 proliferation and collagen deposition? It's quite
10 possible.
11 But advanced fibrosis it doesn't reverse.
12 Whether the inhaled treprostinil has any
13 independent anti-fibrotic properties, we don't
14 know. What we can say about the post hoc analysis
15 from the INCREASE study was that it was
16 hypothesis-generating and now we're testing that
17 hypothesis in the Teton program.
18 Q. So based on that, is it fair to say
19 that you believe the majority of the treatment
20 effects that you saw an increase for inhaled
21 treprostinil are due to treatment of the PH
22 component?
23 ATTORNEY DYKHUIS: Object to form.
24 THE WITNESS: I believe that's
25 much more likely.

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1 BY ATTORNEY DAVIES:
2 Q. Prior to the INCREASE study, did you
3 believe inhaled treprostinil would be safe in the
4 PH-ILD patient population?
5 ATTORNEY DYKHUIS: Object to form.
6 THE WITNESS: We didn't know, and
7 that's why spirometry, which captures
8 FVC, was included as a safety endpoint.
9 BY ATTORNEY DAVIES:
10 Q. So was the INCREASE study designed
11 to assess the impact of inhaled treprostinil on the
12 PH component of PH-ILD?
13 ATTORNEY DYKHUIS: Objection to
14 form.
15 THE WITNESS: It was designed to
16 evaluate if it had clinical benefit. It
17 wasn't designed to test PH, because
18 otherwise we would have had to write off
19 that as our primary endpoint.
20 BY ATTORNEY DAVIES:
21 Q. Was the INCREASE study designed to
22 evaluate the clinical benefit of inhaled
23 treprostinil in the PH component of PH-ILD?
24 ATTORNEY DYKHUIS: Object to form.
25 THE WITNESS: The thought was that

1 BY ATTORNEY DAVIES:
2 Q. Was the INCREASE study designed to
3 evaluate the treatment effects of inhaled
4 treprostinil on the fibrosis component of PH-ILD?
5 ATTORNEY DYKHUIS: Object to form.
6 THE WITNESS: No, it wasn't.
7 BY ATTORNEY DAVIES:
8 Q. Why not?
9 A. Because at that time before the
10 study we had no notional idea that it might have
11 independent anti-fibrotic properties.
12 Q. And even after the INCREASE study,
13 you can't say with certainty whether or not
14 treprostinil has anti-fibrotic properties and
15 that's why you're conducting additional studies;
16 correct?
17 ATTORNEY DYKHUIS: Object to the
18 form.
19 THE WITNESS: That's correct.
20 It's been shown in animal models that it
21 might have anti-fibrotic properties. But
22 whether or not that translates into human
23 subjects remains to be determined by the
24 Teton study.
25

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1 if it were to have benefit, it would be
2 through the PH component, yes.
3 BY ATTORNEY DAVIES:
4 Q. Was it designed to actually assess
5 that, though? Was it powered to assess that?
6 ATTORNEY DYKHUIS: Objection to
7 form.
8 THE WITNESS: The clinical
9 benefit, yes.
10 BY ATTORNEY DAVIES:
11 Q. Sitting here today, what treatments
12 that are approved for Group 1 PH have you
13 prescribed in your Group 3 PH patients?
14 ATTORNEY DYKHUIS: Objection to
15 form.
16 THE WITNESS: I have to go through
17 them all in my head. I mentioned
18 Sildenafil. Certainly not riociguat.
19 Not inhaled iloprost. We don't use
20 anti-receptive antagonists.
21 (Reporter clarification)
22 Q. Maybe just let me reask my question
23 and we'll just try to go through a little bit
24 slower.
25 So what treatments approved for Group 1

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1 pulmonary hypertension have you prescribed for
2 Group 3 patients?

3 ATTORNEY DYKHUIS: Objection to
4 form.

5 THE WITNESS: Without going
6 through the exhaustive list of available
7 therapies, Sildenafil, as I mentioned.
8 Inhaled treprostinil, IV treprostinil,
9 and maybe subcutaneous treprostinil. And
10 maybe tadalafil, t-a-d-a-l-a-f-i-l.

11 BY ATTORNEY DAVIES:

12 Q. With respect to IV treprostinil, did
13 you give that to a Group 3 patient prior to
14 receiving the results of the INCREASE study?

15 ATTORNEY DYKHUIS: Objection to
16 form.

17 THE WITNESS: IV and subcutaneous
18 treprostinil are given parenchymally,
19 which means subcutaneously or
20 intravenously. Those we reserve for the
21 most severe form of hypertension, so
22 these were patients clearly below the
23 Group 1 PAH component but had some lung
24 disease in the context of that. Those
25 are the patients who got those therapies.

1 BY ATTORNEY DAVIES:

2 Q. You prescribed that in those
3 patients prior to receiving the results of the
4 INCREASE study; correct?

5 A. Correct.

6 ATTORNEY DYKHUIS: Object to form.

7 Q. With Tadalafil, did you prescribe
8 that in Group 3 patients prior to receiving the
9 results of the INCREASE study?

10 ATTORNEY DYKHUIS: Object to form.

11 THE WITNESS: Probably so.

12 There's very little data on Tadalafil.
13 And I might have mentioned it because I
14 might have. As I mentioned, Sildenafil
15 was more about go to PDE5 inhibitor.
16 Tadalafil is just a more convenient
17 version of a PDE5 inhibitor given once a
18 day versus three times a day.

19 BY ATTORNEY DAVIES:

20 Q. In your opinion, are there any
21 hemodynamic changes that would be indicative of an
22 improvement in exercise capacity for a PH-ILD
23 patient?

24 ATTORNEY DYKHUIS: Objection to
25 form.

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1 THE WITNESS: None.

2 BY ATTORNEY DAVIES:

3 Q. In your opinion, do hemodynamic
4 changes have any predictive benefit in suggesting
5 an improvement in exercise capacity for a PH-ILD
6 patient?

7 ATTORNEY DYKHUIS: Objection.

8 THE WITNESS: I apologize.

9 BY ATTORNEY DAVIES:

10 Q. That's no problem at all.

11 A. I just want to note that I
12 apologized for the cough. I don't know if you
13 capture a cough, but I was apologizing for the
14 record. For the record, I'm coughing a lot, and I
15 apologize for that.

16 Q. Not a problem. Would you like me to
17 repeat the question?

18 A. Yes.

19 Q. So in your opinion, do hemodynamic
20 changes have any predictive value in suggesting an
21 improvement in exercise capacity for a PH-ILD
22 patient?

23 ATTORNEY DYKHUIS: Object to form.

24 THE WITNESS: What I would say is
25 that they do have somewhat of a

1 predictive capability in the more severe
2 patients that I just described to you.
3 The ones who are so severe that they
4 require parenchymal therapy.

5 So when you have very high
6 pressure in a high pulmonary vascular
7 resistance there's a greater likelihood
8 and certainly a greater hope that we will
9 see some benefit.

10 Otherwise, for more general
11 population of PH-ILD, most of whom have
12 more mild to moderate pulmonary
13 hypertension, they are generally
14 unpredictable.

15 (Discussion held off the
16 record.)

17 ATTORNEY DAVIES: We can keep
18 going until lunch and we can take a
19 break? It's another 30 minutes?

20 ATTORNEY DYKHUIS: Sure.

21 BY ATTORNEY DAVIES:

22 Q. And if you decide that was a bad
23 decision and you want to break before then, you can
24 let me know.

25 A. Yeah.

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1 Q. Is six-minute walk distance a
2 measure of increased exercise capacity?
3 ATTORNEY DYKHUIS: Objection to
4 form.
5 THE WITNESS: We regard it as a
6 surrogate for what patients might be
7 capable of doing. So the answer to that
8 would be yes.
9 BY ATTORNEY DAVIES:
10 Q. Other than six-minute walk distance,
11 are there any other measures of increased exercise
12 capacity?
13 ATTORNEY DYKHUIS: Object to form.
14 THE WITNESS: There are things
15 like cardiopulmonary exercise testing.
16 There are --
17 BY ATTORNEY DAVIES:
18 Q. I'm sorry, go ahead.
19 A. There are patient report outcomes
20 where we ask them about how much they can do. The
21 other test that we generally go to, like the Shekel
22 test, and so there are various forms of evaluating
23 exercise. But the six-minute walk is the most
24 commonly accepted one in terms of what we do in the
25 clinic and in clinical trials.

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1 they're taking six, nine, 12 risks that
2 some of the drug is getting down versus
3 one hit of the DPI, one cough, and the
4 drug comes out.
5 So I think it's the most reliable
6 way of treating these patients that I do
7 use both, depending on the individual
8 patient. But you can well imagine
9 someone coughing right after they get the
10 DPI and they get into drug.
11 BY ATTORNEY DAVIES:
12 Q. Do you have a sense for the percent
13 of patients that you started on Tyvaso DPI that
14 have switched back to the Tyvaso nebulized
15 formulation?
16 ATTORNEY DYKHUIS: Object to form.
17 THE WITNESS: 25, 30 percent. I'm
18 guessing, though, that it's not one of
19 two.
20 BY ATTORNEY DAVIES:
21 Q. Are you familiar with the Dreamboat
22 device?
23 ATTORNEY DYKHUIS: Object to form.
24 THE WITNESS: I am not.
25

1 Q. Are you currently using inhaled
2 treprostinil to treat PH-ILD patients?
3 A. Yes.
4 Q. Are you using nebulized Tyvaso to
5 treat PH-ILD patients?
6 ATTORNEY DYKHUIS: Object to form.
7 THE WITNESS: Nebulized and the
8 dry powder inhaler.
9 BY ATTORNEY DAVIES:
10 Q. Have you seen any switching in your
11 PH-ILD patients who you've started on the dry
12 powder inhaler switching to the nebulized Tyvaso?
13 A. Yes.
14 Q. And why do you think that is
15 occurring?
16 ATTORNEY DYKHUIS: Object to form.
17 THE WITNESS: They sometimes don't
18 tolerate it. Sometimes because it's one
19 breath, especially in the context of
20 interstitial lung disease, they might not
21 be able to take a deep breath to get the
22 drug down into the areas you want it.
23 So in some patients I feel more
24 comfortable using the nebulized version
25 because I feel more assured that at least

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1 BY ATTORNEY DAVIES:
2 Q. Are you aware that the Dreamboat is
3 the dry powder inhaler that's used for Tyvaso DPI?
4 ATTORNEY DYKHUIS: Object to form.
5 THE WITNESS: I'm familiar with
6 the DPI for Tyvaso. I didn't know if it
7 was called the Dreamboat.
8 BY ATTORNEY DAVIES:
9 Q. In your opinion, is the DPI for
10 Tyvaso a high-resistance device?
11 ATTORNEY DYKHUIS: Objection to
12 form.
13 THE WITNESS: I believe it is a
14 high-resistance device.
15 BY ATTORNEY DAVIES:
16 Q. What is a high-resistance device?
17 ATTORNEY DYKHUIS: Object to form.
18 THE WITNESS: I've never
19 researched it myself, to be honest, but I
20 suspect when they take a breath in, it's
21 more of a resistance to taking the breath
22 in versus a low-resistance device.
23 BY ATTORNEY DAVIES:
24 Q. Why do you believe that the Tyvaso
25 DPI device is a high-resistance device?

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<p>1 ATTORNEY DYKHUIS: Object to form. 2 THE WITNESS: I have no idea. 3 BY ATTORNEY DAVIES: 4 Q. Okay. What, in your opinion, is a 5 pulsed inhalation device? 6 ATTORNEY DYKHUIS: Objection to 7 form. 8 THE WITNESS: One that's not 9 continuous, that it comes out in one 10 pulse. 11 BY ATTORNEY DAVIES: 12 Q. Is the Tyvaso DPI a pulse inhalation 13 device? 14 ATTORNEY DYKHUIS: Objection to 15 form. 16 THE WITNESS: I believe it is 17 regarded as such. 18 BY ATTORNEY DAVIES: 19 Q. And what is that belief based on? 20 A. That you actuate it, and it comes 21 out as a pulse while the patient is taking a breath 22 in. 23 Q. When you say you actuate it, you're 24 equating the breath in with the pulse; is that 25 correct?</p>	<p>1 ATTORNEY DYKHUIS: Object to form. 2 THE WITNESS: I'm assuming it is. 3 BY ATTORNEY DAVIES: 4 Q. But you don't know for certain; 5 correct? 6 ATTORNEY DYKHUIS: Object to form. 7 THE WITNESS: I think it's a good 8 assumption. 9 BY ATTORNEY DAVIES: 10 Q. Okay. But you don't know for 11 certain; correct? 12 ATTORNEY DYKHUIS: Object to form. 13 THE WITNESS: I don't know the 14 technicalities of when the pulse comes 15 out versus when the patient takes the 16 breath in. I've never taken a hit 17 myself. I might have, you know, on a 18 placebo device when it first came out, 19 but I don't know technically how the 20 pulse relates to the breath going in. 21 BY ATTORNEY DAVIES: 22 Q. Have you ever -- sitting here today, 23 do you recall any publication where you referred to 24 a dry powder inhaler as a pulse inhalation device? 25 ATTORNEY DYKHUIS: Object to form.</p>
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<p>1 THE WITNESS: I've written many 2 things over the years, and it could be 3 something where there's something about a 4 pulse inhalation device, but I don't 5 recall if I did or I didn't. 6 BY ATTORNEY DAVIES: 7 Q. And sitting here today, you can't 8 recall any presentation that you've given where 9 you've referred to a dry powder inhaler as a pulsed 10 inhalation device; correct? 11 ATTORNEY DYKHUIS: Object to form. 12 THE WITNESS: I've given many 13 presentations. And I don't know if I 14 have or I haven't. I may have. 15 BY ATTORNEY DAVIES: 16 Q. Sitting here today you can't recall 17 any particular circumstance; correct? 18 ATTORNEY DYKHUIS: Object to form. 19 THE WITNESS: That's correct. 20 Q. Do you know whether the Tyvaso DPI 21 pulses the drug independently of the patient's 22 inhalation? 23 ATTORNEY DYKHUIS: Object to form. 24 THE WITNESS: No, the patient has 25 got to be taking a breath in for the</p>	<p>1 pulse to occur. Otherwise, you know, 2 they would be walking around with it in 3 their pocket and it would go off. So 4 there's got to be something to activate 5 the device. 6 BY ATTORNEY DAVIES: 7 Q. Do you consider the nebulizer that's 8 provided with Tyvaso to be a pulsed inhalation 9 device? 10 ATTORNEY DYKHUIS: Object to form. 11 THE WITNESS: My understanding is 12 that it's more continuous. That's my 13 understanding. 14 BY ATTORNEY DAVIES: 15 Q. What is that understanding based on? 16 ATTORNEY DYKHUIS: Object to form. 17 THE WITNESS: The fact that it's a 18 nebulizer, which are generally 19 continuous. Whether there are little 20 pulses in the context of that nebulizer, 21 I don't know, but I've always regarded 22 nebulizers to be more continuous. 23 BY ATTORNEY DAVIES: 24 Q. And you have never seen the dry 25 powder inhaler for Yutrepia; correct?</p>

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1 ATTORNEY DYKHUIS: Object to form.
2 THE WITNESS: Not that I can
3 recall.
4 BY ATTORNEY DAVIES:
5 Q. You've never seen any schematics or
6 drawings of the dry powder inhaler for Yutrepia;
7 correct?
8 A. I believe I might have.
9 Q. Okay. When do you believe you might
10 have?
11 ATTORNEY DYKHUIS: Object to form.
12 THE WITNESS: There might be a
13 picture in my declaration. I thought
14 there was something from the proposed
15 label. Let's see if I'm correct. I
16 thought there was. I could be wrong.
17 No.
18 I thought there might be a little
19 picture of it on this label, but there
20 isn't. My apologies.
21 I might have -- you know, it's
22 been around for all these years, I can't
23 answer to if I haven't Googled an image
24 before, so I probably have, but I'm not a
25 hundred percent certain.

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1 resistance.
2 BY ATTORNEY DAVIES:
3 Q. What do you think it's a function
4 of?
5 ATTORNEY DYKHUIS: Form.
6 THE WITNESS: Just general
7 tolerability. Every patient is
8 different, and there could be an
9 irritation of the particles.
10 I would hypothesize if you have a
11 low-resistance device and suddenly you
12 get a rush of the particles to the back
13 of your throat, that might induce more
14 coughing and perhaps make patients less
15 tolerable of the device.
16 BY ATTORNEY DAVIES:
17 Q. In your clinical practice, how do
18 you determine whether there's been an improvement
19 in exercise capacity in your patients?
20 ATTORNEY DYKHUIS: Objection to
21 form.
22 Q. Let me restate that.
23 In your PH patients, how do you determine
24 whether there has been an improvement in
25 exercise-type capacity?

1 BY ATTORNEY DAVIES:
2 Q. Okay. Sitting here today, you have
3 no knowledge of whether the Yutrepia DPI provides
4 the powder continuously or in pulses in any way;
5 correct?
6 ATTORNEY DYKHUIS: Object to form.
7 THE WITNESS: My assumption is if
8 it's a dry powder, then it should be
9 pulsed, that's my assumption.
10 BY ATTORNEY DAVIES:
11 Q. But you can't say with certainty
12 because you've never seen the device or seen it
13 described; correct?
14 ATTORNEY DYKHUIS: Object to form.
15 THE WITNESS: That's correct.
16 BY ATTORNEY DAVIES:
17 Q. You mentioned that the Tyvaso DPI,
18 in your opinion, was a high-resistance device. Do
19 you believe that you would see less switching if
20 patients were provided with a low-resistance DPI
21 with the same efficacy?
22 ATTORNEY DYKHUIS: Objection to
23 form.
24 THE WITNESS: No idea. I don't
25 think it's necessarily a function of the

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1 ATTORNEY DYKHUIS: Objection to
2 form.
3 THE WITNESS: Talking to the
4 patients always helps in terms of what
5 they can do versus what they used to be
6 able to do. And then we look at the
7 six-minute walk test, and that gives us
8 an idea of what the exercise capabilities
9 are.
10 BY ATTORNEY DAVIES:
11 Q. What information would a patient
12 provide you, short of performing a six-minute walk
13 test, that would inform you as to improvement of
14 the exercise capacity?
15 ATTORNEY DYKHUIS: Object to form.
16 THE WITNESS: They might come in
17 and say, Gosh, Doc, thanks for that
18 medicine. I feel so much better. Before
19 I got shortness of breath going to the
20 bathroom, and now I can go to the
21 bathroom and get the mail that I couldn't
22 do before. That's really dependent on
23 the individual patient.
24 BY ATTORNEY DAVIES:
25 Q. What is an exacerbation of

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1 interstitial lung disease?

2 A. I believe you asked that earlier,
3 but just to reiterate, our form of the definition
4 from our society where it's a worsening of
5 shortness of breath over approximately a four-week
6 period accompanied by worsening oxygenation,
7 accompanied by increased infiltrates on chest
8 imaging, and ruling out other potential causes for
9 this such as heart failure, for example.

10 Q. And how would you determine whether
11 there had been a reduction in one of those
12 exacerbations?

13 ATTORNEY DYKHUIS: Object to form.

14 THE WITNESS: You cannot determine
15 that on an individual patient basis. It
16 takes large studies, much like we had in
17 INCREASE where you compare the one group
18 to the other to see what the incidence is
19 in the one group versus the other.

20 So on an individual patient you
21 can't know if you're having any impact on
22 preventing acute exacerbations.

23 BY ATTORNEY DAVIES:

24 Q. So in a patient you couldn't
25 determine whether or not you were improving an

1 exacerbation. You would need to look at a large
2 study population to do that; correct?

3 ATTORNEY DYKHUIS: Object to the
4 form.

5 THE WITNESS: What you just said
6 is a little bit different. Prevention
7 versus treatment, which is what you just
8 alluded to, I think.

9 Treatment of acute exacerbations
10 is very, very difficult. What we saw in
11 the INCREASE study was fewer acute
12 exacerbations. So less incidence of
13 acute exacerbations versus as a treatment
14 for acute exacerbation.

15 BY ATTORNEY DAVIES:

16 Q. We talk about FVC. Could you tell
17 me what FVC stands for?

18 ATTORNEY DYKHUIS: Object to form.

19 THE WITNESS: Forced vital
20 capacity.

21 BY ATTORNEY DAVIES:

22 Q. What is forced vital capacity?

23 A. It's the amount of air that a
24 patient can blow out after taking a full
25 inspiration and then blowing out as hard as they

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1 can until they can't blow out anymore. That would
2 be the forced vital capacity.

3 Q. And how would you determine in a
4 patient that there has been an improvement in
5 forced vital capacity?

6 A. There's some inherent variability
7 around the forced vital capacity as much as
8 10 percent. So if there's a 3 percent improvement,
9 we don't know if it's test-test variability or if
10 it's real.

11 When we get beyond the 10 percent number,
12 either up or down, then you can be more certain
13 that the change you're seeing is real.

14 Q. So if you're seeing less than a
15 10 percent change in forced vital capacity in a
16 patient, you personally would not be confident that
17 that's a real change; correct?

18 ATTORNEY DYKHUIS: Objection.

19 THE WITNESS: Like everything
20 else, it's a spectrum. Nine percent is
21 more of a change than 1 percent, so
22 there's no definite cutoff. And
23 11 percent is worse than 10 percent, but
24 we typically regard 10 percent as a
25 threshold of a meaningful change. But it

1 could be that changes of less than
2 5 percent are meaningful, but because
3 it's a spectrum it's not as meaningful as
4 a 10 percent change.

5 BY ATTORNEY DAVIES:

6 Q. In the INCREASE study, do you recall
7 to the extent there was a change in FVC if that was
8 greater than or less than 3 percent?

9 ATTORNEY DYKHUIS: Objection to
10 form.

11 THE WITNESS: Are you talking
12 about the difference to the placebo arm?

13 BY ATTORNEY DAVIES:

14 Q. Correct.

15 A. I don't recall what that exact
16 number was. I do recall that it was statistically
17 significant. The 5 percent, 10 percent quality is
18 for the individual patient. For a population-based
19 study where you have many contributors, you can
20 have a change as small as 1 or 2 percent which
21 might be statistically significant.

22 Q. But you could not determine whether
23 there had been a -- let me restart here.

24 You couldn't determine in a patient whether
25 there had been a statistically significant

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1 difference in FVC; correct?

2 ATTORNEY DYKHUIS: Object to the
3 form.

4 THE WITNESS: No. As I mentioned
5 previously, you can't determine
6 statistically -- statistical significance
7 in an individual patient.

8 ATTORNEY DAVIES: I'm going to
9 move to some other stuff. Do you want to
10 take a break for lunch now, because I
11 think we have to grab something.

12 ATTORNEY DYKHUIS: Sounds good.

13 THE VIDEOGRAPHER: We are off the
14 record at 11:51.

15 (Recess taken from 11:51 a.m
16 to 12:46 p.m.)

17 THE VIDEOGRAPHER: We are on the
18 record at 12:46.

19 BY ATTORNEY DAVIES:

20 Q. Welcome back, Doctor. I'm just
21 going to grab two documents here.

22 So I'm marking as Exhibit Number 3 a
23 publication entitled "Controlled Trial of
24 Sildenafil and Advanced Idiopathic Pulmonary
25 Fibrosis" by Zisman, et al., and bearing production

1 number UTC_PH-ILD_010830 to -838.

2 (Exhibit 19 was marked for
3 identification.)

4 Q. And, Doctor, I'm going to ask for
5 your help in passing a copy to counsel as well.

6 A. (Witness complies with request.)

7 Q. My first question for you is have
8 you seen Exhibit 3 before?

9 A. Yes, I have.

10 Q. And what is Exhibit 3?

11 A. It's a report of a controlled trial
12 of "Sildenafil and Advanced Idiopathic Pulmonary
13 Fibrosis" published in the New England Journal of
14 Medicine in 2010.

15 Q. If you turn to page 627 of this
16 paper, and it's near the bottom of the page the
17 author says, "Although the study did not meet its
18 prespecified primary outcome and the therapeutic
19 efficacy of Sildenafil is far from established, our
20 data provides the clinical equipoise needed to
21 conduct further trials involving patients with
22 advanced idiopathic pulmonary fibrosis."

23 Do you see that?

24 ATTORNEY DYKHUIS: Object to form.

25 THE WITNESS: I'm sorry. Where

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1 about did you say it was?

2 BY ATTORNEY DAVIES:

3 Q. If you go to the bottom of the first
4 column --

5 A. Okay.

6 Q. -- do you see there's a sentence
7 that says, "Although this study"?

8 A. Yes.

9 Q. And then if you continue on to the
10 next column, it refers to the data providing the
11 clinical equipoise regarding the trials. What is
12 clinical equipoise?

13 A. Equipoise to me always means the
14 balance, clinical balance, so they're suggesting
15 that there should be further trials involving
16 patients with advanced IPF.

17 Q. And does this study examine the
18 impact of Sildenafil in six-minute walk distance in
19 patients with advanced idiopathic pulmonary
20 fibrosis?

21 ATTORNEY DYKHUIS: Object to form
22 and foundation.

23 THE WITNESS: Yes, it did.

24 BY ATTORNEY DAVIES:

25 Q. Is this study referred to as the

1 STEP-IPF study in your report?

2 ATTORNEY DYKHUIS: Object to form.

3 THE WITNESS: Yes.

4 Q. I'm now going to enter as Nathan
5 Exhibit 4 an article entitled "Sildenafil Preserves
6 Exercise Capacity in Patients with Idiopathic
7 Pulmonary Fibrosis and Right-sided Ventricular
8 Dysfunction" published in Chest by Han et al. in
9 June of 2013.

10 (Exhibit 4 was marked for
11 identification.)

12 Q. Doctor, have you seen this paper
13 before?

14 A. Yes, I have.

15 Q. What is this?

16 A. This paper, as best I recall, was a
17 subgroup analysis of the STEP-IPF study in those
18 patients who had echocardiographic evidence of
19 right ventricular dysfunction.

20 Q. So in the Chest publication, are
21 they describing an evaluation of a subgroup of the
22 patients within the STEP-IPF trial that was
23 described in Exhibit 3?

24 ATTORNEY DYKHUIS: Object to the
25 form and foundation.

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1 THE WITNESS: I'd have to check,
2 but I don't think they talked about the
3 STEP study, which is a post hoc study in
4 the paper that was published in the New
5 England Journal, and I think that I
6 mentioned that, and I would need to read
7 the paper to be certain about that.

8 BY ATTORNEY DAVIES:

9 Q. But you agree that Exhibit 2 is a
10 subgroup study of the earlier STEP-IPF Zisman
11 publication; correct?

12 ATTORNEY DYKHUIS: Object to form.

13 THE WITNESS: Yes, I do.

14 BY ATTORNEY DAVIES:

15 Q. And with respect to this subgroup
16 analysis, I'm looking on the first page of
17 Exhibit 62, in the -- under Results, do you see the
18 Results section in that box?

19 ATTORNEY DYKHUIS: Object to form.

20 THE WITNESS: Yes, I do.

21 BY ATTORNEY DAVIES:

22 Q. So at least with this subgroup of
23 subjects, the authors report, "In the subgroup of
24 subjects with RVSD, subjects treated with
25 Sildenafil experienced less detriment in six-minute

1 walk distance, 99.3 meters, P equals .01 and
2 greater improvement in SGRQ and EuroQol analog
3 scores than subjects receiving placebo."

4 Do you see that?

5 A. I do.

6 ATTORNEY DYKHUIS: Object to form.

7 Q. Okay. I apologize. Just so it's --
8 and I screwed up the exhibit number, so just to
9 make it clear, I apologize. I was referring to
10 Exhibit 4 instead of Exhibit 62.

11 So in Exhibit 4 you would agree that the
12 authors with respect to this subgroup are reporting
13 a significantly -- a statistically significant
14 improvement in six-minute walk distance with
15 treatment of Sildenafil as compared to placebo;
16 correct?

17 ATTORNEY DYKHUIS: Object to form.

18 THE WITNESS: That's what they're
19 reporting on, yes.

20 BY ATTORNEY DAVIES:

21 Q. They also report a significantly --
22 a statistically significant improvement in SGRC
23 within this subgroup as well; correct?

24 ATTORNEY DYKHUIS: Object to form.

25 THE WITNESS: SGRQ, yes.

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1 BY ATTORNEY DAVIES:

2 Q. And they also report a statistically
3 significant improvement in the EuroQOL visual
4 analog scores within this subgroup of patients from
5 the larger STEP-IPF study; correct?

6 ATTORNEY DYKHUIS: Object to form.

7 THE WITNESS: Yes.

8 BY ATTORNEY DAVIES:

9 Q. So at least with respect to the
10 subgroup of patients that are further analyzed in
11 the Chest publication in Exhibit 4, the STEP-IPF
12 trial showed safety and efficacy; correct?

13 ATTORNEY DYKHUIS: Object to form.

14 THE WITNESS: I disagree with
15 that.

16 BY ATTORNEY DAVIES:

17 Q. Why.

18 A. Let me draw your attention to the
19 primary publication, and in terms of the methods,
20 if you go to the methods, if you go to page 621,
21 the last paragraph.

22 "The trial was conducted in two periods:
23 Period 1 was a 12-week double-blind
24 placebo-controlled study of Sildenafil. Period 2
25 was a 12-week open-label extension with all

1 patients on Sildenafil."

2 Now, draw your attention to Table 3.

3 Q. I'm sorry, Doctor. Which are we --

4 A. Still the primary publication.

5 Q. Okay.

6 A. Table 3, this was an intent to treat
7 analysis of mortality. So patients were analyzed
8 in whichever group they were originally assigned
9 to.

10 So if you look numerically, they were at
11 week 28. There were four deaths in the Sildenafil
12 arm, 11 deaths in the placebo arm. So it looks
13 like numerically Sildenafil does better than
14 placebo because this is an intent to treat.

15 Sometimes I say intent to treat is intent
16 to trick. I'll show you the trick here. The trick
17 is that all patients on placebo were switched to
18 Sildenafil. So the additional deaths in the
19 placebo arm were on Sildenafil. There were seven
20 additional deaths. So safety, no.

21 When you do a post hoc analysis, you are
22 taking out patients who died or dropped out, and at
23 best I would say that Chest paper is hypothesis
24 generating. But these numbers if they had analyzed
25 the patients on therapy, the number of deaths would

<p style="text-align: right;">Page 150</p> <p>1 have switched. There would have been 11 on 2 Sildenafil and four on placebo, and that's why I 3 disagree. 4 Sometimes you have studies that have 5 discordant outcomes. They might make patients feel 6 better, but patients can die earlier. 7 Q. The New England Journal of Medicine 8 paper at Exhibit 3 looks like it was published in 9 2010; correct? 10 A. Correct. 11 Q. And you mentioned that you used 12 Sildenafil in the treatment of PH-ILD patients; 13 correct? 14 A. Correct. 15 Q. And did you continue to do so after 16 the publication of this study in 2010? 17 ATTORNEY DYKHUIS: Object to form. 18 THE WITNESS: I did if they had PH 19 of sufficient severity. Another point 20 around this is we don't know which of 21 these patients have pulmonary 22 hypertension because they didn't have 23 riociguat. This was a study in advanced 24 IPF, not in patients with PH and IPF. 25</p>	<p style="text-align: right;">Page 151</p> <p>1 BY ATTORNEY DAVIES: 2 Q. Going back to Exhibit 4, which is 3 the Chest paper. You would agree though, that with 4 respect to the subgroup reported on, in Exhibit 4, 5 these patients did appear to have a significant 6 increase in their six-minute walk distance of 7 nearly 100 meters; correct? 8 ATTORNEY DYKHUIS: Object to the 9 form. 10 THE WITNESS: After the patients 11 who died dropped out and weren't analyzed 12 and you take a specific subgroup, that's 13 what's reported in the paper. 14 BY ATTORNEY DAVIES: 15 Q. Have you ever heard of the term 16 "patient phenotyping"? 17 A. Yes. 18 Q. What's patient phenotyping? 19 A. That's looking at the chemical 20 characteristics of patients that bind them together 21 in terms of having specific clinical 22 characteristics that warrant them being considered 23 as a separate group. 24 Q. And what role does patient 25 phenotyping play in -- let me ask you this. Did</p>
<p style="text-align: right;">Page 152</p> <p>1 patient phenotyping play any role in the design of 2 the INCREASE trial? 3 ATTORNEY DYKHUIS: Object to form. 4 THE WITNESS: I wouldn't 5 characterize it as patient phenotyping. 6 Patients had to have pulmonary 7 hypertension associated with interstitial 8 lung disease. If you want to call 9 patients who are associated with 10 pulmonary hypertension in a patient with 11 interstitial lung disease phenotyping, 12 then you can make that argument. 13 Let me follow that up as well by 14 saying that STEP-IPF in the subgroup 15 analysis grew to be short-term. The one 16 study that you brought to my attention 17 earlier, which was Sildenafil plus 18 pirfenidone, which was a long term study, 19 showed no difference between the groups. 20 So the longer term even if you 21 infer that there was some kind of benefit 22 from this, another robust randomized 23 control study did not validate that these 24 effects were -- you know, there were any 25 long-term benefits.</p>	<p style="text-align: right;">Page 153</p> <p>1 BY ATTORNEY DAVIES: 2 Q. Do you know whether the patients 3 that you've treated with -- strike that. 4 Do you know whether the PH-ILD patients 5 you've treated show an improvement in six-minute 6 walk distance? 7 ATTORNEY DYKHUIS: Object to form. 8 THE WITNESS: Some of them do and 9 some of them don't. 10 ATTORNEY DAVIES: I've marked as 11 Exhibit 5 a publication titled "riociguat 12 for Idiopathic Interstitial 13 Pneumonia-Associated Pulmonary 14 Hypertension, (RISE-IIP): A randomized 15 Placebo-Controlled Phase 2B Study." 16 (Exhibit 5 was marked for 17 identification.) 18 ATTORNEY DAVIES: I'm sorry, just 19 for clarity of the record, it bears Bates 20 numbers UTC_PH-ILD_010530 to -540. 21 BY ATTORNEY DAVIES: 22 Q. And, Doctor, what is this 23 publication? 24 A. This is a report on the randomized 25 controlled study of riociguat for idiopathic</p>

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<p>1 interstitial pneumonia associated with pulmonary 2 hypertension, which was a randomized double-blind 3 controlled, placebo-controlled study. 4 Q. And this is the RISE IIP study that 5 you've described earlier today? 6 A. That's correct. 7 Q. And this is the RISE IIP study 8 that's talked about in your declaration? 9 A. Correct. 10 Q. And there's a Steven D. Nathan 11 that's the first author on this publication. Is 12 that you? 13 A. That would be me. 14 Q. You've testified that you believe 15 that the study was a failure. Is that correct? 16 ATTORNEY DYKHUIS: Object to form. 17 THE WITNESS: I wouldn't 18 characterize it as a failure. It was 19 successfully completed. The drug didn't 20 work and appeared to be harmful to 21 patients, but study itself was a very 22 well-done study. 23 BY ATTORNEY DAVIES: 24 Q. At the time -- why was the trial 25 stopped?</p>	<p>1 ATTORNEY DYKHUIS: Object to form. 2 THE WITNESS: The trial was 3 stopped -- every study such as this 4 randomized control study has a dataset 5 for the monitoring committee. You look 6 at the data, blind it and, you know, 7 sometimes blind and sometimes not, making 8 sure that there's no harm, no foul to the 9 individuals that have entered and 10 continue to be enrolled in the study. 11 And that's a safeguard for patient 12 safety. 13 And that effect, the monitoring 14 committee meets every couple of months, 15 looks at the data and decided when they 16 looked at the data at one point that 17 there was a signal of harm in the 18 riociguat arm that warranted 19 discontinuation of the study. 20 BY ATTORNEY DAVIES: 21 Q. Why, in your opinion, did you see 22 the safety signals that required the study to be 23 stopped? 24 ATTORNEY DYKHUIS: Object to form. 25 THE WITNESS: If you go Table 2 --</p>
Page 156	Page 157
<p>1 BY ATTORNEY DAVIES: 2 Q. Which page is that on, Doctor? 3 A. -785. 4 Q. Yes. 5 A. And you look at the main phase of 6 the study and you see in the last horizontal 7 deaths, you can see that in the main phase of the 8 study there were eight deaths on riociguat and 9 three on placebo, which numerically by itself is 10 not a big difference. And any time a death 11 happens, a monitoring committee recommends halting 12 a study, they wouldn't be fairly certain of what's 13 going on. 14 But then what happened is after the main 15 phase, all patients were placed on long-term 16 open-label extension. 17 Now go across to Column C and 4, and we see 18 one death in the real arm and eight deaths in the 19 former placebo arm. In other words, patients who 20 are dying who were previously on placebo and then 21 rolling over to receive open-label riociguat. 22 And there were more patients coming through 23 the study who are going over from placebo to get 24 riociguat. So the dataset monitoring committee did 25 the right thing in informing us and getting us to</p>	<p>1 hold the study. 2 This goes actually back to the STEP-IPF 3 study, because this was on treatment mortality. If 4 STEP had done on treatment mortality those numbers, 5 as I mentioned, would have flipped around and might 6 have looked similar to this. 7 Q. Okay. Do you believe you saw the 8 safety issues because of the -- you had the wrong 9 patient population in the study? 10 ATTORNEY DYKHUIS: Object to form. 11 THE WITNESS: That might have been 12 a part of it. 13 BY ATTORNEY DAVIES: 14 Q. Riociguat was given to these 15 patients orally; is that correct? 16 A. That's correct. 17 Q. So it would have had systemic 18 effects? 19 ATTORNEY DYKHUIS: Object to form. 20 THE WITNESS: That's correct. 21 BY ATTORNEY DAVIES: 22 Q. If you go to page 781 and you see a 23 little shaded box here in your paper that says, 24 "Research in context." 25 A. Yes.</p>

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1 Q. Do you see there's a reference, it's
2 about half the way down, to a small phase 2
3 randomized control study of riociguat suggested a
4 beneficial response.

5 Do you see that?

6 A. Yes.

7 Q. It's about halfway down in the first
8 column.

9 A. I see small phase two, yes, I see
10 that.

11 Q. What study are you referring to
12 there?

13 ATTORNEY DYKHUIS: Object to form.

14 THE WITNESS: It was a study that
15 had as the first author Marius Hoeper,
16 H-o-3-p-e-r. I want to say it was
17 published in the European Respiratory
18 Journal, but I'm not a hundred percent
19 certain about that.

20 BY ATTORNEY DAVIES:

21 Q. And why did you choose to discuss
22 that publication in your paper on riociguat?

23 A. I want to provide a context for why
24 riociguat was studied in this study, and that's
25 phase 2 -- I would revise the phase 2A study,

1 provided scientific rationale for why it did not
2 work in the study that we did.

3 And this is an example of Rio can -- will
4 treat pulmonary hypertension or lower the
5 pressures, but it was harmful to patients. So you
6 have to divorce treating pulmonary hypertension
7 away or from clinical benefit.

8 Q. In your declaration, you talk about
9 when you presented the results of this RISE-IIP
10 study you were, quote, admonished by one of the
11 session heads.

12 Do you remember saying that?

13 A. I do.

14 Q. Other than being admonished by that
15 one session head, did anyone else at the meeting
16 admonish you for conducting this study with
17 riociguat?

18 A. I don't recall that. As I said, I
19 found the people in the audience, none of the other
20 chairs jumped to my defense. You know, you could
21 construe silence as complicity.

22 I do remember that Mario Succa [phon.]
23 himself was sitting in the front row, and he tried
24 to defend, you know, having done the study because
25 he was the first author on the study that laid the

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1 foundation for the study.

2 But, yeah, I don't know what other people
3 are feeling, but the chairperson who was the
4 chairperson in that session who was renowned leader
5 in the PH field, and he might have influenced
6 people in the field to believe what he espoused,
7 and that was that we shouldn't be treating PH
8 associated with lung disease.

9 Q. And in your report at Paragraph 84
10 you state that the session lead told you, "Everyone
11 knows that treating pulmonary hypertension
12 associated with lung disease does not work."

13 Do you see that?

14 A. I remember that, yes.

15 Q. And other than this one session
16 chair, no one else at this meeting of over 500
17 participants expressed that view to you; correct?

18 ATTORNEY DYKHUIS: Object to form.

19 THE WITNESS: There was a lot of
20 discussion afterwards and people coming
21 up to me. I suspect that people were of
22 that belief, and he had said what he
23 said. There was probably no further need
24 to come up and admonish me. The work had
25 been done.

1 BY ATTORNEY DAVIES:

2 Q. Did anyone else at the meeting come
3 up and admonish you for the work?

4 ATTORNEY DYKHUIS: Object to form.

5 THE WITNESS: No one else came up
6 to me, but I do believe that this thought
7 leader, highly regarded in the PH field,
8 probably reflects the views of many other
9 people he was speaking for. It might not
10 have just been speaking for himself. He
11 might have been speaking for many other
12 people, and he probably influenced a
13 bunch of the people in the audience who
14 ended up being the same after the
15 session.

16 You have a negative study that
17 harmed patients, and then the session
18 lead, who is a very renowned figure in
19 the PH world, admonishing me for thinking
20 that treating PH and ILD could never
21 work, and this should never have been
22 done.

23 BY ATTORNEY DAVIES:

24 Q. Who was the session lead who
25 admonished you?

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1 A. Dr. Lewis Rubin.
2 Q. You had mentioned that this
3 earlier -- this earlier paper by Hooper laid the
4 foundation for your RISE study; correct?
5 ATTORNEY DYKHUIS: Object to form.
6 THE WITNESS: That's correct.
7 BY ATTORNEY DAVIES:
8 Q. Okay. And in what way did that
9 study lay the foundation for your RISE study?
10 ATTORNEY DYKHUIS: Object to form.
11 THE WITNESS: It showed that Rio
12 could potentially be a treatment modality
13 for patients with pulmonary hypertension
14 associated with interstitial lung
15 disease.
16 BY ATTORNEY DAVIES:
17 Q. After your RISE study, do you
18 personally still believe that in the way patient
19 population Rio could be used for treatment of
20 PH-ILD?
21 A. I can't rule it out. But I wouldn't
22 start it in any patient. There could be one in 10
23 patients, but I don't want to knock off another
24 three patients to find that one in 10 patient.
25 Q. When you say "one in 10 patients,"

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1 pick out some of the results from the
2 study like some of the secondary
3 endpoints and say, Yeah, it benefited
4 there, and maybe this is a therapy that
5 you can consider, but it didn't prove
6 anything. It was hypothesis-generating.
7 Let me qualify that. The Hooper
8 article was proof of concept as well, and
9 then subsequently we had a follow-up
10 study that went the other way and proved
11 to be harmful.
12 So proof of concept don't always
13 equate to a positive study and can result
14 in a negative study.
15 BY ATTORNEY DAVIES:
16 Q. So when you used the term "proof of
17 concept" with respect to a clinical study, what do
18 you intend that to mean?
19 ATTORNEY DYKHUIS: Object to form.
20 THE WITNESS: As proof that the
21 concepts of what you're trying to treat
22 with what you're trying to treat must be
23 a beneficial therapy. It's the concept
24 that subsequently remains to be further
25 tested.

1 what one in 10 patients do you believe it would be
2 likely to work in for PH-ILD?
3 ATTORNEY DYKHUIS: Object to
4 form.
5 THE WITNESS: I'm hypothesizing
6 and speculating. I'm giving an example.
7 Any medication that's harmful, it might
8 be the odd patient that it's helpful, but
9 we suspended it because we would harm
10 more patients than helping. And those
11 are the medications that are generally
12 population-based regarded as harmful even
13 though there might be one or two patients
14 who actually benefit.
15 BY ATTORNEY DAVIES:
16 Q. Can you go back to Exhibit 3, which
17 should be the Zisman, et al, paper.
18 A. Yes.
19 Q. And do you agree that this STEP-IPF
20 study described in this publication showed the
21 proof of concept for using a Group 1 therapy
22 Group 3 PH?
23 ATTORNEY DYKHUIS: Object to form.
24 THE WITNESS: You can take proof
25 of concept -- let me say that you could

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1 BY ATTORNEY DAVIES:
2 Q. And when -- what would be required
3 in your mind to show that a proof of concept study
4 actually results in treatment? Does that require a
5 phase 3 placebo-controlled randomized trial?
6 A. Correct.
7 ATTORNEY DYKHUIS: Object to form,
8 foundation.
9 Q. I'm going to pass you two documents,
10 Doctor. The first is Exhibit 6, titled
11 "Nintedanib."
12 (Exhibit 6 was marked for
13 identification.)
14 A. Okay.
15 Q. It's titled "Nintedanib."
16 A. Correct.
17 Q. Plus Sildenafil inpatients with
18 idiopathic pulmonary fibrosis. The first author is
19 Martin Kolb published in the New England Journal of
20 Medicine 2018, bearing Bates numbers beginning
21 UTC_PH-ILD 010487.
22 And I'm also going to pass you Exhibit 7,
23 which is Supplementary Appendix and refers to the
24 New England Journal that I just identified as
25 Exhibit 6. I'm going to pass you that.

<p style="text-align: right;">Page 166</p> <p>1 (Exhibit 7 was marked for 2 identification.) 3 ATTORNEY DYKHUIS: Wait. 4 Exhibit 6? 5 ATTORNEY DAVIES: Exhibit 6 is the 6 New England Journal of Medicine article, 7 and then Exhibit 7 is the supplementary 8 appendix to that same article. 9 ATTORNEY DYKHUIS: Thank you. 10 ATTORNEY DAVIES: Okay. 11 BY ATTORNEY DAVIES: 12 Q. So have you seen Exhibit 6 before, 13 Doctor? 14 A. Yes, I have. 15 Q. And does Exhibit 6 describe the 16 end-stage study that's discussed in your 17 declaration? 18 ATTORNEY DYKHUIS: Object to form. 19 THE WITNESS: Yes, it does. 20 BY ATTORNEY DAVIES: 21 Q. And if you look at Exhibit 7, is 22 Exhibit 7 the Supplementary Appendix that the 23 authors provided along with the publication of 24 their article in the New England Journal of 25 Medicine in Exhibit 6?</p>	<p style="text-align: right;">Page 167</p> <p>1 ATTORNEY DYKHUIS: Object to form 2 and foundation. 3 THE WITNESS: Yes, it is. 4 BY ATTORNEY DAVIES: 5 Q. What were the authors -- what drug 6 was being examined in the end-stage study that's 7 described in Exhibit 6? 8 A. Sildenafil. 9 Q. In what patient population was it 10 being examined in? 11 ATTORNEY DYKHUIS: Object to form. 12 THE WITNESS: Patients with 13 idiopathic pulmonary fibrosis who are on 14 Nintedanib. 15 BY ATTORNEY DAVIES: 16 Q. Would that include PH-ILD patients? 17 ATTORNEY DYKHUIS: Object to form. 18 THE WITNESS: It might. It 19 doesn't look for PH. But there might 20 have been some patients in there who had 21 PH. 22 BY ATTORNEY DAVIES: 23 Q. What was the measure that they used 24 for the primary outcome in the end-stage study 25 described in Exhibit 6?</p>
<p style="text-align: right;">Page 168</p> <p>1 ATTORNEY DYKHUIS: Object to form. 2 THE WITNESS: The primary endpoint 3 was changed from baseline in the total 4 score in St. George's Respiratory 5 Questionnaire at week 12. 6 BY ATTORNEY DAVIES: 7 Q. And did that show an improvement? 8 Did they see an improvement in the use of that 9 questionnaire after treatment with Sildenafil or 10 not? 11 A. No, they did not. 12 Q. Okay. Can you turn to Exhibit 7. 13 A. I've got it. 14 Q. Can you turn to Figure S3. 15 A. (Witness complies with request.) 16 Yes. 17 Q. What is described in Figure S3 of 18 the Exhibit 7 supplementary appendix? 19 ATTORNEY DYKHUIS: Objection to 20 form and foundation. 21 THE WITNESS: This is a figure 22 depicting the two arms of the study 23 looking at change from baseline in the 24 UCSD shortness of breath questionnaire at 25 the time from zero to 24 weeks.</p>	<p style="text-align: right;">Page 169</p> <p>1 BY ATTORNEY DAVIES: 2 Q. So if the authors had used the UCSD 3 shortness of breath questionnaire, do you agree 4 that their treatment with Sildenafil would have 5 shown an improvement over placebo? 6 ATTORNEY DYKHUIS: Object to form. 7 THE WITNESS: That is, I would 8 say, speculative. 9 BY ATTORNEY DAVIES: 10 Q. Why do you say it's speculative? 11 A. Once you choose your primary 12 endpoint, you are a prisoner of your primary 13 endpoint. If you have 20 secondary endpoints in a 14 clinical study, invariably one of them is going to 15 be positive and you can go back and say, If we had 16 chosen this as our primary, this would have been a 17 positive study. This is, once again, 18 baseline-generated. 19 Q. They use the same data in Figure S3, 20 though, that they use for their analysis using the 21 St. George's respiratory questionnaire; correct? 22 ATTORNEY DYKHUIS: Object to form. 23 Excuse me. 24 THE WITNESS: You have to direct 25 me to that figure so I can compare them</p>

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<p>1 off the primary. Actually, it's right</p> <p>2 next to it. It's Figure S2.</p> <p>3 BY ATTORNEY DAVIES:</p> <p>4 Q. Right.</p> <p>5 A. So you're asking me the same</p> <p>6 analysis in Figure S3 is the same as S2?</p> <p>7 Q. Correct.</p> <p>8 ATTORNEY DYKHUIS: Object to form.</p> <p>9 THE WITNESS: It's the same</p> <p>10 analysis, but based on the primary, there</p> <p>11 wasn't a significant difference between</p> <p>12 the two arms.</p> <p>13 BY ATTORNEY DAVIES:</p> <p>14 Q. Why do you believe that there was a</p> <p>15 significant difference if analasized using the UCSD</p> <p>16 shortness of breath questionnaire when there was</p> <p>17 not with the St. George's respiratory questionnaire</p> <p>18 in this study?</p> <p>19 ATTORNEY DYKHUIS: Object to form,</p> <p>20 foundation.</p> <p>21 THE WITNESS: They asked -- these</p> <p>22 are both what we call PROs, patient</p> <p>23 reported outcomes that ask very different</p> <p>24 questions. So it really depends on the</p> <p>25 questions that are asked and how the</p>	<p>1 patients answer them.</p> <p>2 So it's entirely feasible that one</p> <p>3 can show a difference and the other one</p> <p>4 does not.</p> <p>5 BY ATTORNEY DAVIES:</p> <p>6 Q. Can you turn to Figure F5.</p> <p>7 A. S5 or F5?</p> <p>8 Q. S5, I mean. Still on Exhibit 7 in</p> <p>9 the appendix.</p> <p>10 Do you see that?</p> <p>11 A. I do.</p> <p>12 Q. What is shown in Figure S5?</p> <p>13 ATTORNEY DYKHUIS: Objection to</p> <p>14 form.</p> <p>15 THE WITNESS: It's a change from</p> <p>16 baseline in FVC over time. And the two</p> <p>17 treatment arms Nintedanib --</p> <p>18 (Reporter clarification)</p> <p>19 THE WITNESS: The two treatment</p> <p>20 arms, the one is nintedanib plus</p> <p>21 Sildenafil, and the other one is</p> <p>22 Nintedanib plus placebo, and it's looking</p> <p>23 at FVC over time.</p> <p>24 BY ATTORNEY DAVIES:</p> <p>25 Q. Would you agree that Figure S5 shows</p>
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<p>1 a difference in the change of FVC, which favors the</p> <p>2 combination of Sildenafil and Nintedanib as</p> <p>3 compared to Nintedanib and placebo alone?</p> <p>4 ATTORNEY DYKHUIS: Object to the</p> <p>5 form and foundation.</p> <p>6 THE WITNESS: At first glance I</p> <p>7 can see how you make the deduction, but</p> <p>8 you always have to contextualize it. But</p> <p>9 says this is hypothesis generating and it</p> <p>10 depends on how they did the analysis.</p> <p>11 If you look at the number of</p> <p>12 patients at the bottom, you started out</p> <p>13 from the study, it was 137 versus 136.</p> <p>14 And then as the study progresses at 24</p> <p>15 weeks, you have 109 versus 108.</p> <p>16 So you had patients who dropped</p> <p>17 out, patients who didn't have data points</p> <p>18 to record. Which raises a whole lot of</p> <p>19 questions about what you see in the</p> <p>20 draft. If you look at Nintedanib plus</p> <p>21 Sildenafil, that's 28 patients. How do</p> <p>22 they contribute to the FVC initially</p> <p>23 versus the end.</p> <p>24 If these were the sickest patients</p> <p>25 who dropped out, those 28, if they</p>	<p>1 continued to 24 weeks, they would have</p> <p>2 dragged this curve down. So there are a</p> <p>3 lot of holes in this, and as I said, it's</p> <p>4 at best hypothesis-generating, but you</p> <p>5 have to contextualize it as a post hoc</p> <p>6 analysis. And my best summation is that</p> <p>7 this is hypothesis-generating.</p> <p>8 BY ATTORNEY DAVIES:</p> <p>9 Q. What is the hypothesis that it's</p> <p>10 generating?</p> <p>11 ATTORNEY DYKHUIS: Object to form.</p> <p>12 THE WITNESS: That does Sildenafil</p> <p>13 have some kind of effects on fibrosis.</p> <p>14 But this is a far measure from proving</p> <p>15 anything. It just raises that question.</p> <p>16 So once again, I don't know how</p> <p>17 that dealt with the dropouts. If they</p> <p>18 had imputed zero values, which some</p> <p>19 people do, and assume that there was zero</p> <p>20 that were no longer around if they died,</p> <p>21 would that have dragged the new curve all</p> <p>22 the way down?</p> <p>23 So there are many different ways</p> <p>24 to deal with missing data, but when you</p> <p>25 see that -- I don't know what the percent</p>

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1 is, it's at least 20 percent of the
2 patients have missing data and how that
3 was dealt with can alter these curves
4 pretty dramatically.
5 BY ATTORNEY DAVIES:
6 Q. Can you turn to Figure S7 in the
7 appendix in Exhibit 7?
8 A. Yes.
9 Q. What's shown at Figure S7?
10 ATTORNEY DYKHUIS: Object to form.
11 THE WITNESS: This is change from
12 baseline in brain natriuretic peptide at
13 week 24 between the two groups in the
14 Nintedanib plus Sildenafil arm, the
15 antichromium P was reduced and in the
16 treatment arm -- sorry, in the placebo
17 arm it did go up, getting a difference
18 there of minus 51.3.
19 I'm not sure if this is
20 statistically significant or not. I'm
21 not if they show that in the paper. It
22 looks like the confidence intervals are
23 really quite wide. So I'm not sure if
24 it's of statistical significance or not.
25 I know that they provided a P value to go

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1 A. Let's see if I talk about S7 here.
2 (Pause)
3 A. I see on page 172 that I do talk
4 about the BNP change of baseline. They didn't even
5 provide a P value. I suspect that because it's
6 speculative they weren't allowed to provide a P
7 value. That is not a reason why there wouldn't be
8 a P value here.
9 So I'm not sure if it was statistically
10 significant or not. But actually you can figure it
11 out because 95 percent confidence intervals are
12 minus 85 to minus 17.6. So this isn't outside the
13 confidence interval.
14 So my interpretation of this would be that
15 it's not statistically significant. Hopefully I've
16 got that the right way around.
17 Q. So you would agree it shows a change
18 in the levels -- Figure S7 shows a change in the
19 levels, but you can't say sitting here whether or
20 not it was statistically significant; right?
21 ATTORNEY DYKHUIS: Objection to
22 form.
23 THE WITNESS: The 95 percent
24 confidence intervals include the number
25 minus 51. So my interpretation based on

1 with this.
2 BY ATTORNEY DAVIES:
3 Q. What do you use levels of brain
4 natriuretic peptide for in clinical studies you've
5 participated in for PH?
6 ATTORNEY DYKHUIS: Object to form.
7 THE WITNESS: It's a blood test
8 that's a biomarker, which usually
9 reflects cardiac stress and strain. The
10 higher the level, the more stress the
11 heart is under, and the lower the level,
12 the less stress the heart is in.
13 BY ATTORNEY DAVIES:
14 Q. So would you agree that Figure S7
15 shows that in the Nintedanib plus Sildenafil arm it
16 showed less stress on the heart than the Nintedanib
17 plus placebo alone?
18 ATTORNEY DYKHUIS: Object to form
19 and foundation.
20 THE WITNESS: That is a test and
21 see what they said about Figure 7. I'm
22 just curious to see if it's statistically
23 significant.
24 BY ATTORNEY DAVIES:
25 Q. Sure.

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1 this is that it wasn't statistically
2 significant.
3 BY ATTORNEY DAVIES:
4 Q. So there's a difference, but it's
5 not statistically significant?
6 A. Correct.
7 ATTORNEY DYKHUIS: Object to form.
8 Q. When was the first time that you
9 were optimistic that you were going to get a good
10 result out of the INCREASE trial?
11 ATTORNEY DYKHUIS: Object to form.
12 THE WITNESS: I don't remember.
13 When I saw the results.
14 BY ATTORNEY DAVIES:
15 Q. When was that again.
16 A. It was towards the end of February
17 of 2020.
18 Q. When in your mind during disease
19 progression does PH become a driver for treatment
20 outcomes in PH-ILD patients?
21 ATTORNEY DYKHUIS: Objection to
22 form.
23 THE WITNESS: We don't know that.
24 We hypothesize, though, that when it does
25 occur it becomes the main driver of

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<p>1 outcomes compared to the underlying 2 primary disease, but we don't know that 3 for sure. 4 The two intersect so closely and 5 kind of feed off one another that it's 6 hard to unwind the two from one another 7 is what I would say. 8 BY ATTORNEY DAVIES: 9 Q. You would agree that at some point 10 there's an inflection point where PH becomes the 11 driver of treatment outcomes rather than ILD; 12 correct? 13 ATTORNEY DYKHUIS: Object to form. 14 THE WITNESS: It sounds like 15 you've read a -- you've seen a document 16 that I produced in a couple of journals 17 where I show that exact figure of an 18 inflection point where -- but that's 19 hypothetical. I don't know that for 20 sure. 21 BY ATTORNEY DAVIES: 22 Q. Okay. But you presented on that; 23 correct? 24 ATTORNEY DYKHUIS: Object to form. 25 THE WITNESS: I presented on that</p>	<p>1 because it gives the concept, yes. 2 BY ATTORNEY DAVIES: 3 Q. So the idea that at some point the 4 PH severity reaches a level that the treatment of 5 the PH component becomes the driver for the 6 treatment outcome. Is that what you're trying to 7 convey by that? 8 ATTORNEY DYKHUIS: Object to form. 9 THE WITNESS: That's possible. 10 BY ATTORNEY DAVIES: 11 Q. Okay. Do you agree with that 12 sitting here today? 13 ATTORNEY DYKHUIS: Object to form. 14 THE WITNESS: I think it's more 15 complex than this or that. As I said, 16 the two are so closely intertwined that 17 it's hard to really figure out. But it's 18 possible that the PH is what's driving 19 the outcomes. 20 BY ATTORNEY DAVIES: 21 (Exhibit 8 was marked for 22 identification.) 23 ATTORNEY DAVIES: I'm going to 24 enter as Exhibit 8 a document titled 25 United States Patent 10,716,793 bearing</p>
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<p>1 UTC Bates numbers UTC_PH-ILD-009772 2 through -796. Exhibit 8. 3 Q. And Doctor, is this the '793 patent 4 that you offer opinions on in your report? 5 A. Yes, it appears to be. 6 BY ATTORNEY DAVIES: 7 Q. Do you have any understanding as to 8 whether the '793 patent -- the claims of the '793 9 patent claims a method of treating PH-ILD? 10 ATTORNEY DYKHUIS: Objection to 11 form. 12 THE WITNESS: That is the last 13 page in this Column 18. What it's 14 claiming is a method of treating 15 pulmonary hypertension. So in answer to 16 your question, it states it there. 17 BY ATTORNEY DAVIES: 18 Q. So you would agree that it 19 describes a method of -- 20 A. Sorry, hang on one second. 21 Q. Go ahead. 22 A. A method of treating pulmonary 23 hypertension, it doesn't say interstitial lung 24 disease. So my error. It says a method of 25 treating pulmonary hypertension.</p>	<p>1 Q. Okay. Do you understand that that 2 method of treating pulmonary hypertension described 3 in the '793 patent includes treatment of PH-ILD? 4 ATTORNEY DYKHUIS: Objection to 5 form. Speaks for itself. 6 THE WITNESS: I think there is 7 mentioned somewhere in the patent of 8 treating pulmonary hypertension without 9 being specific to the cause. So I would 10 regard that as any form of pulmonary 11 hypertension. 12 BY ATTORNEY DAVIES: 13 Q. If you look at table 3. Let me know 14 when you're there. Columns 13 and 14. 15 And do you see under the table there's some 16 very small words where it's describing the patient 17 characteristics, hemodynamic parameters and gas 18 exchange values of baseline before challenged with 19 inhalative proteinoids is the title of the table. 20 A. Yes, I see that. 21 Q. And the last little line at the 22 bottom of the table refers to pulmonary fibrosis. 23 A. I see the F. I'm not seeing the 24 legend to say that it's pulmonary fibrosis. Let me 25 see.</p>

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1 Q. Do you see the words right before
2 the F that say "pulmonary fibrosis"?

3 A. I see IOTF. I'm not seeing where it
4 says "pulmonary fibrosis."

5 Q. So, Doctor, go below the table. The
6 very last line there says, "Etiology of pulmonary
7 hypertension was classified as," and then it gives
8 a list of the types of pulmonary --

9 A. Yes.

10 Q. Do you see there that it refers to
11 pulmonary fibrosis?

12 A. Yes.

13 Q. Do you understand that to be PH-ILD?

14 ATTORNEY DYKHUIS: Object to form.

15 THE WITNESS: I'm looking at the
16 pulmonary artery pressure in the top.

17 But it doesn't say that this is the
18 systolic pulmonary artery pressure, the
19 mean pulmonary artery pressure.

20 So I'm a little uncertain. You
21 can have a high systemic pulmonary
22 pressure without having pulmonary
23 hypertension. The PDR, I'm used to
24 operating in wood units. You have to
25 divide these numbers by 80 to see if they

1 have pulmonary hypertension.

2 But the PDRs do look quite high
3 for the group as a whole. What I don't
4 know, though, is if you look at -- let's
5 assume all these patients -- let's assume
6 some of these patients at least might
7 have had pulmonary hypertension. I don't
8 know how many of the four had pulmonary
9 hypertension and what their pressures
10 were.

11 So there's not enough clarity and
12 granularity to this table to make any
13 definitive contribution.

14 BY ATTORNEY DAVIES:

15 Q. Doctor, do you recall --

16 A. Let me make one more point. This
17 is values at baseline before challenge with
18 enolated proteinoids. It's just some baseline
19 values of groups of patients from assumably three
20 different studies. I'm assuming one, two and three
21 refer to three-different studies.

22 Q. In your declaration, do you recall
23 offering opinions that the '327 patent is not
24 invalidated by the disclosure or claims of the '793
25 patent.

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1 Do you recall offering those opinions?

2 A. I do.

3 Q. When you offered those opinions, did
4 you, in your opinion, understand that the '793
5 patent covered a method of treating PH-ILD?

6 ATTORNEY DYKHUIS: Objection to
7 form.

8 THE WITNESS: It was treating any
9 form of pulmonary hypertension, which
10 does include PH associated with
11 interstitial lung disease. But treating
12 pulmonary hypertension is taking a
13 pressure that's high and making it lower.

14 And what we don't know and what
15 I've alluded to is if it can or will
16 result in clinical benefit or if that can
17 or will result in clinical harm and what
18 that clinical benefit may or may not be
19 if, indeed, there is a clinical benefit.

20 So treating pulmonary hypertension
21 does not equate to treating the patient.

22 BY ATTORNEY DAVIES:

23 Q. So is it your opinion that there's
24 not enough data provided in the '793 patent to
25 convince you that it's directed to a method of

1 treating PH-ILD in a patient?

2 ATTORNEY DYKHUIS: Object to form.

3 THE WITNESS: It does talk about
4 treating PH-ILD in a patient, but it
5 doesn't talk about treating the patient.
6 It's saying the pressures are high, we're
7 going to make them lower. What does that
8 mean? Benefit arm neutral, we don't
9 know.

10 BY ATTORNEY DAVIES:

11 Q. What data would you have expected to
12 see in the '793 patent for you to conclude that --
13 you described treating a PH-ILD with inhaled
14 trepostinil?

15 ATTORNEY DYKHUIS: Object to form.
16 Speculation.

17 THE WITNESS: As I just said, it's
18 providing a treatment to the patient.
19 Whether the treatment will be beneficial
20 to the patient is an unknown.

21 It also depends on your -- one's
22 notion of what treatment is. Giving
23 someone a medication is arguably
24 treatment, but is it directed to the
25 question or disease in hand. You need to

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1 make that connection. There's no
2 connection here to having any clinical
3 benefit for the patient, or it just says
4 we have a drug, we'll take a drug, and
5 we'll lower the pressures in the lung,
6 and that's where it ends.

7 BY ATTORNEY DAVIES:

8 Q. So in your opinion, the '793 patent
9 provides no evidence as to a clinical benefit for a
10 patient following administration of an inhaled
11 treprostinil; correct?

12 ATTORNEY DYKHUIS: Object to form.

13 Lack of foundation.

14 THE WITNESS: That would be
15 correct. I mean, there's no mention of
16 any clinical consequence of treating a
17 pulmonary hypertension.

18 BY ATTORNEY DAVIES:

19 Q. If you look at Table 2, and that's
20 at Column 11 in the '793 patent. Just let me know
21 once you're there.

22 A. Yeah.

23 Q. And you see Table 2 has some
24 hemodynamic parameters that compares placebo versus
25 30 micrograms treprostinil, 45 micrograms

1 treprostinil, and 60 micrograms treprostinil.

2 Do you see that?

3 A. Yes.

4 Q. And in your opinion, does Table
5 2 provide any evidence of actually treating the
6 patients with inhaled treprostinil?

7 ATTORNEY DYKHUIS: Objection to
8 form.

9 THE WITNESS: I see the -- once
10 again, I'm uncertain if it's a systolic
11 pulmonary artery pressure or the mean
12 pulmonary artery pressure because they
13 are different. I see the pressures do
14 come down numerically. Whether that's
15 statistically significant or not, I'm not
16 sure.

17 BY ATTORNEY DAVIES:

18 Q. So you reading the '793 patent could
19 not conclude anything about the treatment of a
20 patient with inhaled treprostinil from the data
21 provided in Table 2; correct?

22 ATTORNEY DYKHUIS: Objection to
23 form. Mischaracterizes.

24 THE WITNESS: You can treat a
25 patient with inhaled treprostinil, and

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1 you can cause the pressures to come down.
2 And this might be what you're looking at.
3 Whether it's significant detriment or
4 not, I'm uncertain. There's not enough
5 there yet. So it is treating the
6 pulmonary hypertension, but there's no
7 mention of any kind of clinical benefit.

8 And, once again, sometimes taking
9 the pressures down might impose harm in a
10 patient rather than helping the patient.

11 BY ATTORNEY DAVIES:

12 Q. And what data would you have needed
13 to be provided in the '793 patent to convince you
14 that there was a clinical benefit based on
15 administration of inhaled treprostinil in these
16 patients?

17 ATTORNEY DYKHUIS: Objection to
18 form. Speculation.

19 THE WITNESS: I would need to see
20 the study. I don't know if a patent
21 application is going to convince me that
22 medication is of benefit. I need to see
23 primary study, I think.

24 BY ATTORNEY DAVIES:

25 Q. Would you need a phase

1 3 placebo-controlled randomized trial to conclude
2 that?

3 ATTORNEY DYKHUIS: Same
4 objections.

5 THE WITNESS: Correct.

6 BY ATTORNEY DAVIES:

7 (Exhibit 9 was marked for
8 identification.)

9 Q. This is going to be Exhibit --
10 Doctor, I'm entering as Exhibit 9 a document
11 entitled United States patent 11,826,327 B2,
12 bearing production Number UTC_PH-ILD_005310 through
13 -5360.

14 And, Doctor, is Exhibit 9 the '327 patent
15 that you discussed in your report, your declaration
16 in this case?

17 A. It appears to be.

18 Q. Can you go to the claims of the '327
19 patent, and I'm going to ask you to have the '327
20 patent open to the claims at the end and also the
21 '793 patent, which is Exhibit 8.

22 A. Okay.

23 Q. I want you to specifically look at
24 the dosing that's described in Claim 1 of the '327
25 and the dosing that's described in Claim 1 of the

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1 '793 patent. Just let me know if you've had an
2 opportunity to do that.
3 A. So the '327 says an amount -- an
4 effective amount of at least 50 micrograms up to a
5 maximum accelerated dose, okay.
6 Now, go to the '793, that says effective
7 comprises from 15 to 19.
8 Q. So Claim 1 of both the '327 patent
9 and the '793 patent describe the use of at least 15
10 micrograms of inhaled treprostinil; correct?
11 ATTORNEY DYKHUIS: Object to the
12 form.
13 THE WITNESS: Correct.
14 BY ATTORNEY DAVIES:
15 Q. And then do you see the '327 patent
16 refers to a single administration event that
17 comprises at least six micrograms per breath?
18 A. I see that.
19 Q. And the '793 patent, do you see it
20 refers to one to three breaths?
21 A. I see that.
22 Q. Okay. If I administered -- and you
23 agree that, for example, 18 micrograms would be
24 between 15 and 90 in the '793 patent; correct?
25 ATTORNEY DYKHUIS: Object to form.

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1 Q. Okay. I apologize. And '327 patent
2 also describes the use of six micrograms per
3 breath; correct?
4 ATTORNEY DYKHUIS: Objection to
5 the form. Mischaracterizes.
6 THE WITNESS: Yes.
7 BY ATTORNEY DAVIES:
8 Q. So you would agree that the dosing
9 described in the '793 and the '327 of inhaled
10 treprostinil covers the same dosing regime;
11 correct?
12 ATTORNEY DYKHUIS: Objection to
13 form. Mischaracterizes.
14 THE WITNESS: They appear to
15 overlap. It seems to be limited in one
16 and not limited in the other.
17 BY ATTORNEY DAVIES:
18 Q. But you would agree that they
19 overlap; correct?
20 A. They overlap.
21 Q. Okay. Both in terms of the total
22 amount delivered and the amount given per breath;
23 correct?
24 ATTORNEY DYKHUIS: Object to form.
25 THE WITNESS: They overlap.

1 THE WITNESS: 18 doses between 15
2 and 19.
3 BY ATTORNEY DAVIES:
4 Q. And if I delivered 18 micrograms in
5 accordance with the '793 patent of inhaled
6 treprostinil in three breaths, how many micrograms
7 per breath would I be administering under the '793
8 patent?
9 ATTORNEY DYKHUIS: Objection to
10 form.
11 THE WITNESS: I believe it would
12 be three breaths.
13 BY ATTORNEY DAVIES:
14 Q. I'm sorry. If I delivered 18
15 micrograms -- 18 micrograms of inhaled
16 treprostinil, according to the '793 patent, in
17 three breaths, how many micrograms of treprostinil
18 would I be delivering per breath?
19 ATTORNEY DYKHUIS: Objection to
20 form. Incomplete hypothetical.
21 THE WITNESS: Do you want me to
22 multiply 18 times three?
23 BY ATTORNEY DAVIES:
24 Q. I think it's 18 divided by three?
25 A. I said that. Six.

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1 BY ATTORNEY DAVIES:
2 Q. Do you see that '327 is directed
3 to -- look at Claim 1. So Claim 1 is directed to a
4 method of proof, improving exercise capacity in a
5 patient having pulmonary hypertension associated
6 with interstitial lung disease.
7 Do you see that?
8 A. Yes, I do.
9 Q. Do you believe that Claim 1 of the
10 '793 patent also includes a method of improving
11 exercise capacity in a patient having pulmonary
12 hypertension associated with interstitial lung
13 disease?
14 ATTORNEY DYKHUIS: Object to form.
15 THE WITNESS: That's what it says.
16 ATTORNEY DYKHUIS: Sorry. I note
17 my objection. My objection is to form
18 and foundation.
19 BY ATTORNEY DAVIES:
20 Q. Both the '327 -- both Claim 1 of the
21 '327 patent and Claim 1 of the '793 patent require
22 the administration of inhaled treprostinil;
23 correct?
24 ATTORNEY DYKHUIS: Object to form.
25 THE WITNESS: That's correct.

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1 BY ATTORNEY DAVIES:
2 Q. I'm sorry, Doctor. I don't think
3 your answer came through.
4 A. That's correct.
5 Q. The data that's described in the
6 '327 patent, does this -- was this data from the
7 INCREASE study?
8 ATTORNEY DYKHUIS: Object to the
9 form. Foundation.
10 THE WITNESS: I'm not sure you can
11 call it data. It's a claim that appears
12 to reflect some of the findings from the
13 INCREASE study.
14 BY ATTORNEY DAVIES:
15 Q. Maybe just let me be a little bit
16 more particular.
17 So moving away from the claim, and if you
18 just look through the '327 patent, there is a
19 number of figures that provide resulting data. And
20 then if you look in the specification, flipping
21 through it again, there's data regarding treatment
22 using inhaled treprostinil versus placebo.
23 Is it your understanding that this data in
24 the '327 patent came from the INCREASE study?
25 ATTORNEY DYKHUIS: Objection to

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1 Q. I'm going to mark as Exhibit 10 an
2 abstract bearing the number S343 entitled "Inhaled
3 treprostinil in Group 3 pulmonary hypertension by
4 Agarwal and AV Waxman" and bearing production
5 number UTC_PH-ILD_9828.
6 (Exhibit 10 was marked for
7 identification)
8 ATTORNEY DYKHUIS: Is this a good
9 time for a break?
10 ATTORNEY DAVIES: That's fine.
11 BY ATTORNEY DAVIES:
12 Q. Let me just -- have you seen this
13 before.
14 A. I have.
15 Q. Okay.
16 THE VIDEOGRAPHER: We are off the
17 record at 13:57.
18 (Recess taken from 1:57 p.m.
19 to 2:07 p.m.)
20 THE VIDEOGRAPHER: We are on the
21 record at 2:07 p.m.
22 BY ATTORNEY DAVIES:
23 Q. Going back to the Exhibit 10, which
24 is the Agarwal abstract. Do you have that in front
25 of you?

1 form. Foundation.
2 THE WITNESS: Let me look.
3 There's a lot of data. I'm trying
4 to be sure.
5 A lot of the data is from the
6 INCREASE study, that was your question.
7 I'm looking at something on Table 16,
8 which is not from the INCREASE study.
9 Unless there's other tables amongst the
10 2020 tables, that is from the INCREASE.
11 BY ATTORNEY DAVIES:
12 Q. So sitting here today, you can't say
13 for certain one way or the other; is that fair?
14 ATTORNEY DYKHUIS: Object to form.
15 Q. I'll ask that again with the mic on.
16 So sitting here today, you're not sure one
17 way or another the source of the data in the '327
18 patent, where it came from; correct?
19 A. It seems to be from a number of
20 studies. I see Table 19 there's mention of the
21 TRIUMPH study, for example. It could be increased
22 TRIUMPH, and then I think the switch study -- I
23 forget what it was called -- from Tyvaso ultrasonic
24 nebulizer to Tyvaso DPI. There might be one table
25 from there.

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1 A. Yes.
2 Q. Have you seen this abstract before?
3 A. Yes.
4 Q. Do you cite to this abstract in your
5 declaration?
6 A. Yes, I do.
7 Q. What's the title of this abstract?
8 A. The title is "Inhaled trepostinil in
9 Group 3 pulmonary hypertension."
10 Q. And PH-ILD is a Group 3 pulmonary
11 hypertension?
12 ATTORNEY DYKHUIS: Object to form.
13 THE WITNESS: That's correct.
14 BY ATTORNEY DAVIES:
15 Q. Do you know who AB Waxman is?
16 A. Yes, I do.
17 Q. Who is he?
18 A. Aaron Waxman. I'm not sure what his
19 middle initial stands for.
20 Q. And he's an author on this abstract?
21 A. Yes, he is.
22 Q. Was he also on the steering
23 committee for INCREASE?
24 A. Yes, he is.
25 ATTORNEY DYKHUIS: Object to form.

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1 Q. Do you know Dr. Waxman?
2 ATTORNEY DYKHUIS: Object to form.
3 THE WITNESS: Yes, I do.
4 BY ATTORNEY DAVIES:
5 Q. Would you consider him to be an
6 expert in the treatment of PH-ILD?
7 ATTORNEY DYKHUIS: Object to form.
8 THE WITNESS: I think he has
9 expertise in this area.
10 BY ATTORNEY DAVIES:
11 Q. Who is M. Agarwal?
12 A. I don't know who M. Agarwal is.
13 Q. Do you see the statement in the
14 second sentence of the Purpose says, "Inhaled
15 treprostinil therapy is delivered directly to
16 well-ventilated lung units, preserving VQ, and
17 reducing undesirable alterations in perfusion."
18 Do you see that sentence?
19 A. Yes.
20 Q. Do you agree with that sentence?
21 ATTORNEY DYKHUIS: Object to form.
22 Foundation.
23 THE WITNESS: I would phrase it
24 differently. I think that we theorize
25 that this is something that might happen,

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1 A. That's what's written in the
2 conclusion.
3 Q. Do you see the Methods discussion?
4 A. I see the Methods section, yes.
5 Q. And do you see it describes the
6 dosing starting at three breaths of inhaled
7 treprostinil?
8 ATTORNEY DYKHUIS: Object to form.
9 THE WITNESS: Yes, I've seen it.
10 BY ATTORNEY DAVIES:
11 Q. And it's increased to a goal of 9 to
12 12 breaths four times daily as tolerated.
13 Do you see that?
14 A. I do see that.
15 Q. And you would agree that the dosing
16 of inhaled treprostinil described here overlaps
17 with the dosing described in Claim 1 of the '327
18 patent; right?
19 ATTORNEY DYKHUIS: Object to form.
20 Foundation.
21 THE WITNESS: Yes, I do.
22 BY ATTORNEY DAVIES:
23 Q. You can put that exhibit aside.
24 A. Can I make a comment?
25 Q. You can make a comment if you need

1 and it doesn't happen necessarily in
2 every patient, but it's not definitive as
3 to what happens.
4 BY ATTORNEY DAVIES:
5 Q. If you look under results in this
6 abstract, what is the mean change in the six-minute
7 walk distance that's reported for the group who
8 were administered inhaled treprostinil?
9 ATTORNEY DYKHUIS: Object to form.
10 THE WITNESS: The mean change in
11 the six-minute walk distance was
12 60.85 meters with what looks like a
13 standard deviation of 92.6 meters.
14 BY ATTORNEY DAVIES:
15 Q. And was that a statistically
16 significant improvement?
17 ATTORNEY DYKHUIS: Object to form.
18 THE WITNESS: Based on the P
19 value, it does appear to be statistically
20 significant.
21 BY ATTORNEY DAVIES:
22 Q. And the author concluded in this
23 abstract that Group 3 PH can be effectively and
24 safely treated with inhaled treprostinil.
25 Do you see that?

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1 to.
2 A. I do note here that the pulmonary
3 vascular resistance of the group was 8.7, which is
4 very high. And in this group of patients without
5 having further details about their lung disease,
6 they could potentially be regarded as, you know,
7 more than Group 1 PAH phenotype based on the very
8 high pulmonary vascular resistance, which is
9 different to the mean pulmonary vascular resistance
10 of the patients which entered the INCREASE study
11 which is around four, if I remember correctly.
12 So to your point about phenotypes, it
13 appears to be a phenotype with more severe
14 pulmonary hypertension that could be more
15 successfully treated based on this abstract.
16 Q. But you would agree that the
17 patients in this abstract would have included
18 PH-ILD, you're saying a different subset from those
19 that you examined in INCREASE?
20 ATTORNEY DYKHUIS: Object to form.
21 Mischaracterizes.
22 THE WITNESS: They were -- I want
23 to see the number. They called them
24 restrictive disease. There's a
25 difference between restrictive disease

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<p>1 and interstitial lung disease, which goes 2 to what restriction is in patients who 3 have restricted lung physiology and have 4 reduced FVCs, which could be interstitial 5 lung disease. But there are other things 6 that could give restriction like if you 7 have muscle weakness or if you have 8 tremendous obesity, it can also manifest 9 as restrictive disease. But I would 10 assume for all intents and purposes that 11 most, if not all of these patients, did 12 have interstitial lung disease. 13 BY ATTORNEY DAVIES: 14 Q. I'm going to enter as Exhibit 11 New 15 England Journal of Medicine article entitled 16 "Inhaled Treprostinil in Pulmonary Hypertension Due 17 to Interstitial Lung Disease" published in 2021, 18 first author Waxman, last author Steven D. Nathan, 19 M.D., bearing production number UTC_PH-ILD_010790 20 through -829. 21 Pass to you, Doctor. 22 (Exhibit 11 was marked for 23 identification.) 24 Q. Doctor, what is Exhibit 11? 25 A. Exhibit 11 is a reproduction of a</p>	<p>1 study entitled, "Inhaled treprostinil in pulmonary 2 hypertension due to interstitial lung disease" that 3 was published in the New England Journal of 4 Medicine reflecting the results of the INCREASE 5 study. 6 Q. And Doctor, you mentioned earlier 7 that -- a change in FVC that was observed during 8 the INCREASE study. Can you point me to where in 9 this publication that's described? 10 A. As I recall, and it's been a while, 11 it might just be in the supplements. Let me go 12 straight there and see if I can find it -- I can 13 find it. 14 Q. Doctor, if you go to Table S2, and 15 you can look at whatever you want, but if you go to 16 Table S2, the supplement, it's page 21 of the 17 supplement, does that describe a change in FVC? 18 ATTORNEY DYKHUIS: Object to form. 19 THE WITNESS: It does. No. Hang 20 on a second. This is baseline 21 characteristics so it doesn't. Let's 22 move on. 23 Give me one minute. It looks like 24 it could be in S6. S6, this looks like 25 it. So what we see at week 16 is a</p>
Page 204	Page 205
<p>1 difference in percent predicted at 1.8, 2 which was statistically significant at 3 .03. 4 BY ATTORNEY DAVIES: 5 Q. Doctor, which page is that on? 6 A. I'm sorry, it's page 26, Table S6. 7 Q. You're looking at -- 8 A. At the top you can see FVC and MLs 9 and FVC in percent predicted. 10 Q. So with respect to FVC MLs, was 11 there a difference between the treatment group and 12 the inhaled treprostinil group? I'm sorry. Let me 13 try that again. 14 With respect to FVC milliliters, was there 15 a difference between the group given inhaled 16 treprostinil versus the placebo group? 17 ATTORNEY DYKHUIS: Object to form. 18 THE WITNESS: It was a numeric 19 difference of 44.4 MLs, but it wasn't 20 statistically significant with a P value 21 of 1.21. 22 BY ATTORNEY DAVIES: 23 Q. And with respect to the change in 24 FVC percent predicted, was there a difference 25 between the treprostinil treatment group and the</p>	<p>1 placebo group? 2 ATTORNEY DYKHUIS: Object to form. 3 THE WITNESS: There was a 4 difference of 1.8 percent, which was 5 significant with a P value of .03 at 16 6 weeks. 7 BY ATTORNEY DAVIES: 8 Q. Do you see if you go to the 9 page 326, so out of the supplement but back into 10 the article itself, and I'm looking at page 326. 11 Just let me know once you're there. 12 A. Yes, I'm there. 13 Q. Do you see the statement, it's 14 pretty close to the Methods section at the bottom 15 that says, "The data from previously completed 16 pilot studies suggest that inhaled trepostinil 17 could improve hemodynamics and functional capacity 18 in patients with Group 3 pulmonary hypertension." 19 Do you see that? 20 A. I do. 21 Q. And there's references 9 through 12 22 that are cited there? 23 A. Yes. 24 Q. If you go to the references in the 25 last page of the article. Are you there?</p>

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1 A. I am.

2 Q. And reference 10 refers to an
3 abstract by Agarwal and Waxman. Is that the
4 Agarwal abstract that we've been talking about?

5 ATTORNEY DYKHUIS: Object to form.

6 THE WITNESS: Yes, it appears to
7 be.

8 BY ATTORNEY DAVIES:

9 Q. And for that statement you also
10 relied on a publication by Faria-Urbina entitled
11 "Inhaled Trepstinil and Pulmonary Hypertension
12 Associated with Lung Disease."

13 Do you see that?

14 A. I do see that.

15 Q. Do you agree that you also cited to
16 and relied on a publication by Bajwa, et al,
17 entitled "The Safety and Tolerability of Inhaled
18 Trepstinil in Patients with Pulmonary Hypertension
19 and Chronic Obstructive Pulmonary Disease"
20 published in circulation in 2017?

21 ATTORNEY DYKHUIS: Object to form.

22 THE WITNESS: I see that.

23 Q. And you also relied on a publication
24 by Wang et al entitled "Hemodynamic and Gas
25 Exchange Effects of Inhaled iloprost in patients

1 with COPD and Pulmonary Hypertension" published in
2 the International Journal of Chronic Obstructive
3 Pulmonary Disorders in 2017.

4 Do you see that?

5 ATTORNEY DYKHUIS: Object to form.

6 THE WITNESS: I do see that.

7 BY ATTORNEY DAVIES:

8 Q. Are there any errors in this New
9 England Journal of Medicine article that you're
10 aware of sitting here today?

11 ATTORNEY DYKHUIS: Object to form.
12 Foundation.

13 THE WITNESS: I'm not aware of any
14 errors, but if I may comment on those
15 references.

16 It looks like the paper number 9,
17 a lot of times when you have this, you
18 have an abstract first, you present it at
19 international meeting followed by a
20 paper.

21 So I'm not sure how many of the
22 same patients that were in 10 carried
23 over to 9. There's a chance that this is
24 a report on the same paper -- patients,
25 just that one was reported as an abstract

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1 and the other as a manuscript, and that's
2 not uncommon. The statement that you
3 read is data from previously computed --
4 (Reporter admonition)

5 THE WITNESS: Going back to the
6 statement you previously read, data from
7 previously completed pilot studies
8 suggest that inhaled trepostinil can
9 improve hemodynamics and functional
10 capacity inpatients with Group 3
11 pulmonary hypertension.

12 Two of these papers, the last two
13 appears to be COPD, which is another form
14 of Group 3 pulmonary hypertension. So
15 the reference really to this kind of
16 improvement, this comes back to that one
17 group of patients for the most part in
18 terms of ILD.

19 BY ATTORNEY DAVIES:

20 Q. Those are the group of patients that
21 you believe are described in both the Faria-Urbina
22 publication and the Waxman abstract, which is
23 Exhibit -- the Waxman-Agarwal abstract which is
24 Exhibit 10 that we've introduced already; correct?

25 ATTORNEY DYKHUIS: Object to form.

1 THE WITNESS: Yes, I'm not a
2 hundred percent certain about it, but
3 without having that paper and knowing
4 exactly that it's the same patients, but
5 that's what I suspect because it's not
6 uncommon to have an abstract first
7 followed by a full manuscript.

8 BY ATTORNEY DAVIES:

9 Q. Okay, Doctor. So I'm going to enter
10 three exhibits. The first is Exhibit 12, which if
11 you to the flip to the second page is entitled
12 "Highlights of Prescribing Information" From Tyvaso
13 treprostinil inhalation solution, revised July 2009
14 and bearing production number UTC_PH-ILD_010692 to
15 -708.

16 (Exhibit 12 was marked for
17 identification.)

18 Q. I'm going to also introduce as
19 Exhibit 13 a document entitled "Highlights of
20 Prescribing Information" Tyvaso, treprostinil
21 inhalation solution revised both 03/2021 bearing
22 Bates number UTC_PH-ILD_010744 through-758.

23 (Exhibit 13 was marked for
24 identification.)

25 Q. And the last one, Exhibit 14. If

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1 you turn to the second page after the exhibit
2 cover, it is entitled Highlights of Prescriptions
3 information, Tyvaso DPI for oral administration,
4 revised 06/2023 and bearing production numbers
5 UTC_PH-ILD_010727 through -742. I'll pass these
6 over to you.

7 And let me know when you've had a chance to
8 look at them.

9 (Exhibit 14 was marked for
10 identification.)

11 Q. There should be three there. So
12 Exhibit 12 was the Tyvaso 2009 label.

13 A. Okay.

14 ATTORNEY DAVIES: It says
15 Exhibit 2 on the front. That's how you
16 guys cite it in the report.

17 ATTORNEY DYKHUIS: So 2009.
18 BY ATTORNEY DAVIES:

19 Q. 2009 is Exhibit 12. The 2021 label
20 is Exhibit 13. And the Tyvaso DPI 23 label is 14.

21 Have you had a chance to look at them,
22 Doctor?

23 A. Oh, gosh, do you want me to read all
24 of them, or are you going to direct me where to go?

25 Q. And with respect to Exhibit 12, do

1 you recognize that as the Tyvaso 2009 label for
2 nebulized inhaled Tyvaso?

3 ATTORNEY DYKHUIS: Object to form.

4 Q. And I'll point you to the next page
5 on the second page is the July 2009.

6 A. Yes, I do.

7 Q. And with respect to Exhibit 13, do
8 you agree that that is the 2021 label for nebulized
9 Tyvaso inhalation solution?

10 ATTORNEY DYKHUIS: Objection to
11 form.

12 THE WITNESS: Yes.

13 BY ATTORNEY DAVIES:

14 Q. For Exhibit 14, do you agree that 14
15 is the 2023 label for the Tyvaso DPI product?

16 ATTORNEY DYKHUIS: Object to form.

17 THE WITNESS: Yes.

18 BY ATTORNEY DAVIES:

19 Q. So if you go to the -- let's go
20 to -- sorry. Exhibits 12, 13, and 14 you'll recall
21 are all cited in your declaration in this case;
22 correct?

23 A. I'm sure they probably were, and I
24 feel like I'll need to double check. But if you
25 tell me that they were, then I'm good with that.

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1 Q. If you would like to double-check,
2 that's totally fine.

3 A. I believe that they were.

4 Q. Okay. Going to Exhibit 12, what
5 indication was Tyvaso approved for in 2009 in
6 Exhibit 12?

7 A. It was approved for WHO Group 1
8 pulmonary arterial hypertension and NYHA Class III
9 symptoms.

10 Q. In 2009, was Tyvaso approved for
11 treatment of PH-ILD?

12 A. No, it wasn't.

13 Q. Okay. Can you turn to Exhibit 13,
14 the 2021 Tyvaso label.

15 A. Yes. (Witness complies with
16 request.)

17 Q. Just let me know once you're there.

18 A. I'm there.

19 Q. What was Tyvaso approved for in 2021
20 in the 2021 label of Exhibit 13?

21 A. So the difference in the two labels
22 is that in addition to Group 1 PAH, Tyvaso was then
23 approved in 2021 for pulmonary hypertension
24 associated with interstitial lung disease -- that's
25 PH-ILD -- to improve exercisability.

1 Q. If you look at the dosing section of
2 the 2021 label, you'll agree that the same dosing
3 is used for treatment of both PAH Group 1 and
4 PH-ILD Group 3; correct?

5 ATTORNEY DYKHUIS: Object to form.
6 Foundation.

7 THE WITNESS: That appears to be
8 the case, yes.

9 BY ATTORNEY DAVIES:

10 Q. And you agree that the dosing of
11 inhaled trepostinil in the 2021 Tyvaso label is the
12 same dosing administration described in the 2009
13 label for nebulized Tyvaso; correct?

14 ATTORNEY DYKHUIS: Objection to
15 form. Foundation.

16 THE WITNESS: Let me double-check
17 that. I'm not seeing specific reference
18 to 9 to 12 breaths, yeah, as the
19 recommended dose unless I'm missing it.
20 It gives a dosing table. Sorry, that's
21 the DPI. I'm sorry.

22 BY ATTORNEY DAVIES:

23 Q. No problem. I can ask my question
24 again, if that would be helpful.

25 Do you agree that the dosing of inhaled

<p style="text-align: right;">Page 214</p> <p>1 trepostinil in the 2021 Tyvaso label is the same 2 dosing administration described in the 2009 label 3 for nebulized Tyvaso; correct? 4 ATTORNEY DYKHUIS: Object to form 5 and vague. 6 THE WITNESS: What I'm seeing in 7 the 2009 is maximum recommended dose is 8 nine breaths of Tyvaso four times a day. 9 It says 9 to 12 breaths. So it's not 10 exactly the same. 11 BY ATTORNEY DAVIES: 12 Q. Have you changed the way that you 13 dose Tyvaso to PH patients as compared to 2009? 14 ATTORNEY DYKHUIS: Object to form. 15 THE WITNESS: I wouldn't say so. 16 I didn't use much Tyvaso for PAH. So 17 limited experience for PAH, but certainly 18 a lot of experience with PH-ILD, where 19 typically I'll try and get them to at 20 least nine and preferably 12. And even 21 though that's a dosing recommendation, 22 sometimes we go beyond there. 23 BY ATTORNEY DAVIES: 24 Q. If you go to the 2009 label and go 25 to page 2 at Section 2.1.</p>	<p style="text-align: right;">Page 215</p> <p>1 A. Okay. 2 Q. And do you see there there's a 3 reference to the Tyvaso inhalation system? 4 A. Yes. 5 Q. And it's referred to as the 6 OPTINEB-ir model ON-100/7. 7 Do you see that? 8 A. I do see that. 9 Q. Do you see there that at least the 10 label describes it as a pulse delivery device? 11 A. I do see that, yes. 12 Q. Okay. And that's different than 13 your understanding earlier in the day when you 14 understood the nebulized device to be not a pulse 15 delivery device; correct? 16 A. Yeah, that was my mistake. 17 Q. If you go to Exhibit 14, which is 18 the DPI label. 19 A. (Witness complies with request.) 20 Yes. 21 Q. And in the 2023 label for Tyvaso 22 DPI, what is Tyvaso DPI approved for? 23 A. It's approved for the treatment of 24 pulmonary arterial hypertension as well as 25 pulmonary hypertension associated with interstitial</p>
<p style="text-align: right;">Page 216</p> <p>1 lung disease. 2 Q. And if you look at the dosing and 3 administration section in the 2023 Tyvaso DPI 4 label, do you agree that the same dosing and 5 administration is used for both of those two 6 indications; correct? 7 ATTORNEY DYKHUIS: Object to form. 8 THE WITNESS: It appears to be so. 9 BY ATTORNEY DAVIES: 10 Q. Doctor, I'm going to enter as 11 Exhibit 15 an article from Pulmonary Circulation 12 entitled "The safety and Tolerability of Inhaled 13 Trepostinil in Patients with Pulmonary Hypertension 14 and Chronic Obstructive Pulmonary Disease," first 15 author Aboobacker A. Bajwa bearing Bates number 16 UTC_PH-ILD_009844 through -9852. 17 Doctor, have you seen this paper before. 18 (Exhibit 15 was marked for 19 identification.) 20 A. Let me see if I reference that. I 21 don't recall. Oh, yeah, here we go, yeah. 22 Q. And Doctor, do you recall that this 23 was also one of the publications that was cited in 24 your INCREASE paper as a rationale for the study? 25 ATTORNEY DYKHUIS: Object to form.</p>	<p style="text-align: right;">Page 217</p> <p>1 Foundation. 2 THE WITNESS: It was part of the 3 background. Once again, this is COPD 4 versus ILD, which are entirely different. 5 BY ATTORNEY DAVIES: 6 Q. You as the author, though, did cite 7 it in that INCREASE study publication; correct? 8 A. Correct, as background for potential 9 treatment of Group 3 pulmonary hypertension, not 10 for potential treatment of PH-ILD. And just to 11 contextualize it, even though it's COPD, 12 subsequently inhaled trepostinil has been shown not 13 to work in PH associated with COPD. 14 Q. In your opinion, does this 15 publication justify using inhaled trepostinil for 16 PH-ILD or not? 17 ATTORNEY DYKHUIS: Object to form 18 and foundation. 19 THE WITNESS: No, it does not. 20 BY ATTORNEY DAVIES: 21 Q. Does this paper form any part of the 22 rationale, in your opinion, for the use of inhaled 23 trepostinil in treating PH-ILD? 24 ATTORNEY DYKHUIS: Same objection. 25 THE WITNESS: It formed the</p>

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rationale for studying therapies for Group 3 pulmonary hypertension, which includes both ILD and COPD.

So the concept of treating pulmonary hypertension associated with lung disease was supported, but this was somewhat tangential to ILD because this was COPD, a totally different disease.

BY ATTORNEY DAVIES:

Q. I'm going to enter as Exhibit 16 a publication entitled "Inhaled Trepstinil and Pulmonary Hypertension Associated with Lung Disease," first author Mariana Faria-Urbina, last author Aaron B. Waxman bearing Bates number UTC_PH-ILD_009936 through -09943.

(Exhibit 16 was marked for identification.)

Q. Have you seen this paper before, Doctor?

A. I have seen it before, but I don't believe I saw it in the context of my declaration, but I could be wrong. Let me double-check that.

Sorry. Yes, so it was part of the volume of material that I considered for my declaration.

Q. And this also is one of the

publications that you as an author in the New England Journal of Medicine article for the INCREASE trial cited as rationale for that INCREASE study; correct?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: That is correct.

Part of the foundation for looking at the therapies in Group 3 pulmonary hypertension, yes.

BY ATTORNEY DAVIES:

Q. And this article at what is Exhibit 16 by Faria-Urbina, how did this form the foundation for the INCREASE study?

ATTORNEY DYKHUIS: Objection to form.

THE WITNESS: It provided proof of concept. It was hypothesis-generating that we actually could treat pulmonary hypertension associated with Group 3 with inhaled trepostinil.

BY ATTORNEY DAVIES:

Q. And, in fact, if you look at the results -- strike that.

You would agree that the patient population described in Exhibit 16 in the Faria-Urbina article

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includes PH-ILD; correct?

ATTORNEY DYKHUIS: Object to form. Foundation.

THE WITNESS: Yes, it did.

BY ATTORNEY DAVIES:

Q. Your response was "Yes, it did," Doctor; is that correct?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: I'm double-checking to see exactly what they said with regards to the population, but I'm sure that it did. I just want to see how they state the patients with ILD, how they presented them.

Well, in Table 1 they have inhaled trepostinil as nine of the patients. An additional five with combined pulmonary fibrosis and emphysema.

BY ATTORNEY DAVIES:

Q. So you would agree that the patient population in Faria-Urbina does include PH-ILD patients; correct?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: Correct.

BY ATTORNEY DAVIES:

Q. And if you look at the results on the first page, the authors report a significant improvement in both functional class and six-minute walk distance.

Do you see that?

A. I do.

Q. And that improvement in six-minute walk distance for patients treated with inhaled trepostinil, is that statistically significant?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: It has a P value of .022, which would qualify it as statistically significant.

However, N equals 11, and there were 17 -- 22 patients. So I'm not sure who those 11 patients are they're reporting on. There were 14 and how many of them had interstitial lung disease versus the other condition.

BY ATTORNEY DAVIES:

Q. In your opinion, does this -- this paper in Exhibit 16, does this provide a justification to use inhaled trepostinil for the treatment of PH-ILD patients?

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1 A. No, not at all. Not at all.
2 Q. Not at all?
3 A. No.
4 Q. Why not?
5 A. It's a retrospective study. So
6 arguably there's some bias to retrospective papers.
7 I did point out previously that the pulmonary
8 vascular resistance was quite high and the
9 pulmonary artery pressure was quite high.
10 So these were the patients who were leaning
11 more to Group 1 PH-ILD phenotype. And then
12 whenever you have a retrospective study, you are
13 limited in terms of missing data, and I pointed
14 that out that they reported on the six-minute walk
15 distance of only 11 out of 22 patients. So what
16 happened to the other half and what did they do.
17 How did they treat their members.
18 So I think for all those reasons
19 retrospective, missing data, this is
20 hypothesis-generating. Even the authors themselves
21 say the potential role of PH-specific drugs in
22 Group 3 PH should be further assessed in the larger
23 retrospective study. So they recognize their
24 limitations.
25 Q. Do you know whether Dr. Waxman

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1 negative direction, which underscores the
2 point that I made earlier which is that
3 you cannot use this paper as a
4 justification for treating PH as in the
5 context of pulmonary hypertension.
6 BY ATTORNEY DAVIES:
7 Q. I'm going to enter as Exhibit 17 a
8 paper entitled "Hemodynamic and Gas Exchange
9 Effects on Inhaled iloprost in patients with COPD,
10 Pulmonary Hypertension" by Lan Wang, et al,
11 published in the International Journal of COPD
12 bearing production Number UTC_PH-ILD_010782 through
13 -789.
14 Doctor, have you seen this paper before?
15 (Exhibit 17 was marked for
16 identification.)
17 A. Let me see. Sorry.
18 ATTORNEY DYKHUIS: Excuse me.
19 Could I have a copy?
20 Q. We're asking you to do a lot.
21 That's normally not part of your job doing a
22 deposition, but you're doing fine.
23 A. I preface that, I'm not as sharp as
24 I should be because of this nagging cold and my
25 nasal stuffiness.

1 considered this paper to provide a justification
2 for the INCREASE study?
3 ATTORNEY DYKHUIS: Object to form.
4 Calls for speculation.
5 THE WITNESS: I don't know for
6 sure, but I suspect he did.
7 BY ATTORNEY DAVIES:
8 Q. Did you ever discuss this paper with
9 Dr. Waxman?
10 A. I did not.
11 Q. Why do you suspect that he did
12 believe this was a justification?
13 ATTORNEY DYKHUIS: Object to form.
14 THE WITNESS: Because he had the
15 study. He had the experience of the
16 individual patients, and so I'm sure that
17 he ultimately believed this was a
18 justification for an INCREASE study.
19 And I also believe that there was
20 a justification for the PERFECT study.
21 One worked for out great for ILD, the
22 other one didn't work great for COPD
23 using the same paper as justification.
24 So one went in a positive
25 direction, the other one went to a

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1 Let me see if this is one of the cited
2 references from my report. So this is Wang.
3 Indeed it was.
4 Q. And this was also one of the
5 publications that we looked at earlier that you had
6 cited to in your New England Journal of Medicine
7 INCREASE study publication for support for the
8 rationale of that study; correct?
9 ATTORNEY DYKHUIS: Objection to
10 form.
11 THE WITNESS: That's correct.
12 BY ATTORNEY DAVIES:
13 Q. In your opinion, does this Wang 2017
14 paper provide a justification for using inhaled
15 trepostinil to treat PH-ILD?
16 A. No, not at all.
17 Q. Why not?
18 A. Because this isn't PH-ILD. This is
19 PH COPD.
20 Q. Do you know any of the authors of
21 this study?
22 A. I do not.
23 Q. Did you ever discuss this study with
24 any of the other members of the steering committee
25 for the INCREASE study?

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1 A. I did not. I don't recall
2 discussing this paper at all.

3 Q. Do you believe that this study
4 provides a justification for using inhaled
5 trepostinil in a Group 3 patient population?

6 ATTORNEY DYKHUIS: Object to form.

7 THE WITNESS: No. Not at all.

8 It's a totally different drug. It's
9 iloprost, not trepostinil. Given by a
10 different system. If you have a
11 different drug or a different drug
12 formulation given by a different system,
13 the results can be entirely different
14 than what has been seen or what might be
15 seen with another drug.

16 BY ATTORNEY DAVIES:

17 Q. Do you believe that this publication
18 provides any justification for using a Group 1 PH
19 therapy in a Group 3 PH patient?

20 ATTORNEY DYKHUIS: Object to form.
21 Foundation.

22 THE WITNESS: It does appear to be
23 a reduction in the pulmonary pressures is
24 as much as I can say. Four patients
25 received a single dose of iloprost; it's

1 a nasal dilator. Then there's a bunch of
2 things including the mean pulmonary
3 arterial pressure and the pulmonary
4 vascular resistance and it went down.

5 So what that means is the drug did
6 what it's supposed to do. It's a
7 pulmonary vasodilator with one dose. It
8 has no meaning in terms of clinical
9 benefit, and there's no long-term data
10 here.

11 So this just is very, very -- just
12 adds to the existing literature of what
13 we knew already.

14 BY ATTORNEY DAVIES:

15 Q. Can you go back to Exhibit 15, which
16 is the Bajwa article.

17 A. (Witness complies with request.)
18 Okay.

19 Q. Are you there?

20 A. Yes, sir.

21 Q. In your opinion, does the Bajwa 2017
22 article at Exhibit 15 provide any justification for
23 the use of a Group 1 PH treatment in the treatment
24 of Group 3 PH?

25 ATTORNEY DYKHUIS: Objection to

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1 form and foundation.

2 THE WITNESS: No, it doesn't.
3 It's the same onset, provides a
4 rationale, perhaps, to chase the
5 hypothesis of inhaled trepostinil, and in
6 this case specifically in COPD. But I
7 don't believe that this particular series
8 had any ILD patients.

9 So as I said earlier, this was
10 cited in NJM article for Group 3 as a
11 whole, which includes COPD and ILD. This
12 by itself doesn't really provide
13 justification for treating PH-ILD. It
14 provides a rationale for studying inhaled
15 trepostinil in PA COPD. That study was
16 done and unfortunately was a negative
17 study. And that was a PERFECT study.

18 BY ATTORNEY DAVIES:

19 (Exhibit 18 was marked for
20 identification.)

21 (Discussion held off the
22 record.)

23 Q. Dr. Nathan, I've given you what I've
24 marked as Exhibit 18, a document titled "Safety and
25 Tolerability of High-dose Inhaled Trepostinil in

1 Pulmonary Hypertension," first author Kishan Parikh
2 bearing production number UTC_PH-ILD_010599
3 through -610.

4 Have you seen this publication before,
5 Doctor?

6 A. Yes, I have.

7 Q. And this is the Parikh article that
8 you discussed in your declaration; is that correct?

9 A. That's correct.

10 Q. In your opinion, does the Parikh
11 article provide any justification for the use of
12 inhaled trepostinil in the treatment of PH-ILD?

13 A. No, it does not.

14 ATTORNEY DYKHUIS: Object to form.

15 Q. Why not?

16 A. Because there's no evidence of any
17 efficacy of clinical improvement, or their primary
18 endpoint was that it was safe and tolerable. But
19 there, once again, are holes in any study that's
20 retrospective and single-centered.

21 So basically it's just going back through I
22 don't know how many charts in cobbling the data
23 together and putting this paper together. For that
24 very reason all I can say is it was safe and
25 tolerable but there's no evidence of efficacy.

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1 If you look, for example, there were a
2 total of 80 patients, 31 -- 32 percent -- 31.6 to
3 be exact, had PH secondary to lung disease. 31.6.
4 Then if you're looking for any efficacy measure,
5 they do report the six-minute walk at follow-up
6 visits one and two.

7 There's no set time interval. This is just
8 the average time interval, 5.2 minutes is a wide
9 range, and 20 minutes was an even wider range. And
10 let's see what they said for the walk distance.

11 Something in here. Efficacy, six-minute
12 walk, okay. Average change was 3.9 X from baseline
13 to follow app. Out of 80 patients, there were 39.
14 So what happened to the other 41? Did that drop
15 out all the patients with PH ILD? We have no idea.

16 These could all be patients with PH, for
17 all we know. And 31.6 meters sounds great, but
18 what happened to the risk of the dropouts and who
19 were the patients who dropped out and who were the
20 ones that were included?

21 So there's always inherent bias to a
22 retrospective study. Obviously the patients who we
23 followed up on are the ones probably going to stick
24 on the drug and probably going to do well. So
25 there's inherent bias to the patients who were less

1 than 50 percent, and here we have I think 34
2 patients out of 80 who managed to stick on drug and
3 eventually eke out -- not eke out, have a
4 difference in the six-minute walks of 31.6 meters.

5 But that's why you need the randomized
6 control studies to account for the patients who
7 drop out, the patients who die, and for the
8 patients to be blinded to therapy.

9 If we go back to the INCREASE study, there
10 were patients in the placebo arms who had
11 improvements in their numbers. So we don't know,
12 once again, if this is a drug effect or if this is
13 something else that's going on in these patients.
14 We don't know how many of these patients went into
15 pulmonary rehab, for example.

16 Pulmonary rehab will improve the six-minute
17 walk distance. That's why you need the rigors of a
18 randomized control study where patients can't
19 leave. They can't initiate pulmonary rehab during
20 the course of the study. So this really is totally
21 uninformative in terms of efficacy.

22 Q. Do you know any of the authors on
23 the Parikh publication in Exhibit 18?

24 A. I do. I know Victor Tapson. He was
25 one of the steering committee members together with

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1 myself and Aaron Waxman. And I do know Abby Poms.

2 Q. Do you know whether Dr. Tapson
3 believed that this article formed a justification
4 for the use of inhaled trepostinil in PH-ILD?

5 ATTORNEY DYKHUIS: Object to form.
6 Speculation.

7 THE WITNESS: I can't speak for
8 him. There's a good chance that he might
9 have. I don't know.

10 BY ATTORNEY DAVIES:

11 Q. Did you ever talk to -- strike that.
12 Who is Abbe D. Poms?

13 A. Abby Poms is a coordinator there. I
14 think she is involved in the pulmonary rehab
15 program at Duke. I'm not sure if she's still at
16 Duke or not.

17 Can I take that back. I think she's the
18 pulmonary hypertension coordinator at Duke or was.

19 Q. That's Abby Poms?

20 A. Abby Poms, yes.

21 Q. Do you know if United Therapeutics
22 funded this study at Exhibit 18, the Parikh
23 publication?

24 ATTORNEY DYKHUIS: Objection to
25 form and foundation.

1 THE WITNESS: It does say at the
2 end, Acknowledgments, that it was funded
3 by United Therapeutics as well as an NIH
4 grant.

5 BY ATTORNEY DAVIES:

6 Q. I'm introducing as Exhibit 19 a
7 document entitled "United States Patent Application
8 publication" to Wade et al, Publication Number U.S.
9 2013/0096200 A1 and bearing production numbers
10 UTC_PH-ILD_010774 through -781.

11 (Exhibit 19 was marked for
12 identification.)

13 Q. My first question, and I see you're
14 already looking, is have you seen this document
15 before?

16 A. Yes, I have.

17 Q. And is this one of the documents
18 that you relied on in your declaration?

19 A. Yes, it is.

20 Q. Who was the applicant for this
21 United States patent application?

22 ATTORNEY DYKHUIS: Object to form.

23 THE WITNESS: United Therapeutics
24 Corporation.
25

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1 BY ATTORNEY DAVIES:
2 Q. Then you see some inventors listed
3 below there?
4 A. Uh-huh.
5 Q. Do you know Michael Wade?
6 A. I do not. I meet a lot of people.
7 I might have met him at some point.
8 Q. Do you know Stewart Rich?
9 A. I do know Stewart Rich, yes.
10 Q. Who is Stewart Rich?
11 A. He's a PH expert and cardiologist in
12 the Chicago area.
13 Q. Does he work for United
14 Therapeutics?
15 A. At one point he did, but at this
16 time I don't believe he does.
17 Q. Do you know Eugene Sullivan?
18 A. I do know Eugene Sullivan.
19 Q. Who is that?
20 A. He's a physician. I believe he's a
21 pulmonologist by training. He used to be with FDA
22 and then United Therapeutics, and now he's with
23 another company.
24 Q. Do you know Robert Roscigno?
25 A. I do know Robert Roscigno, yes.

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1 the heading "Field" for paragraph 2?
2 A. Yes.
3 Q. And paragraph 2 states, "The
4 invention relates to the use of treprostinil or
5 its derivatives or pharmaceutically acceptable salt
6 thereof to treat and/or prevent interstitial lung
7 disease or asthma or a condition associated with
8 interstitial lung disease or asthma."
9 Do you see that?
10 A. I do.
11 Q. Is PH-ILD a condition associated
12 with interstitial lung disease?
13 ATTORNEY DYKHUIS: Objection to
14 form.
15 THE WITNESS: Yes, it is.
16 BY ATTORNEY DAVIES:
17 Q. If you look at paragraph 17, let me
18 know once you're there.
19 A. Yes.
20 Q. Okay. It states, "The current
21 invention relates to therapies that enhance blood
22 flow by increasing blood flow through smaller
23 vessels and capillaries and are effective to treat
24 and prevent interstitial lung disease or conditions
25 associated with interstitial lung disease such as

1 Q. Who is Robert Roscigno?
2 A. He used to have been with United
3 Therapeutics, and he's moved around a little bit.
4 I know that he has Liquidia -- with Liquidia and
5 I'm not sure currently, it was a while ago that I
6 knew him. I haven't seen him for a long time.
7 Q. Have you ever worked with Robert
8 Roscigno?
9 A. I've never worked directly with him,
10 no.
11 Q. Have you ever been involved in any
12 clinical studies with Robert Roscigno?
13 A. Not that I recall. As you can tell
14 from my CV when you went through it, there was some
15 funding from UT many few years ago. I can't
16 remember when exactly I met him. And it was
17 involving a study somewhere.
18 Q. Do you know Roger Jeffs?
19 A. I do know Roger Jeffs, yes.
20 Q. Who is Roger Jeffs?
21 A. Roger Jeffs is the former CEO of
22 United Therapeutics and to my understanding the
23 current CEO of Liquidia.
24 Q. If you flip over to, I guess, page 1
25 of this application and look at the -- do you see

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1 pulmonary fibrosis."
2 Do you see that?
3 A. Yes.
4 Q. So do you understand this patent
5 application be directed to treatments for
6 conditions associated with interstitial lung
7 disease including PH-ILD?
8 ATTORNEY DYKHUIS: Objection to
9 form.
10 THE WITNESS: Actually, I have a
11 slightly different take on that, because
12 when they say "such as pulmonary
13 fibrosis," what they mean by "conditions
14 associated with interstitial lung
15 disease" appears to be conditions
16 associated under the broad banner of
17 interstitial lung disease.
18 Otherwise they might have said
19 pulmonary hypertension, which is more
20 like a complication rather than discrete
21 clinical entities under the broad
22 umbrella of interstitial lung disease.
23 BY ATTORNEY DAVIES:
24 Q. You understand that's just an
25 example, though, and it doesn't limit the

<p style="text-align: right;">Page 238</p> <p>1 associated conditions for interstitial lung 2 disease, correct? 3 ATTORNEY DYKHUIS: Objection to 4 form. Vague. 5 THE WITNESS: I do understand 6 that, and they could have put other 7 conditions like connective tissue-related 8 pulmonary fibrosis, scleredema-related 9 pulmonary fibrosis. So to me they -- I 10 can understand when it says conditions 11 associated with interstitial lung disease 12 you can go one of two ways. Are they 13 talking about condition under the banner 14 of ILD or conditions associated as 15 comorbidities with the ILD. 16 That seems like the broad group of 17 conditions and the ILD that I can see how 18 someone else might interpret this is 19 well, maybe this could include pulmonary 20 hypertension, but that wouldn't have been 21 my interpretation of this. My 22 interpretation would have been what I 23 described. 24 BY ATTORNEY DAVIES: 25 Q. If you go to Paragraph 30.</p>	<p style="text-align: right;">Page 239</p> <p>1 A. Uh-huh. 2 Q. Do you see it says, "The present 3 invention encompasses methods of using treprostinil 4 or its derivatives or pharmaceutically acceptable 5 salts thereof." 6 Do you see that? 7 A. I do. 8 Q. So this patent application is 9 directed to the use of treprostinil as a treatment? 10 ATTORNEY DYKHUIS: Objection to 11 form. 12 THE WITNESS: Yes. 13 BY ATTORNEY DAVIES: 14 Q. If you go to Paragraph 37, it's on 15 page 3, second column. 16 A. Okay. 17 Q. In Paragraph 37 it's describing some 18 formulations of the invention. 19 Do you see that? 20 ATTORNEY DYKHUIS: Objection to 21 form. 22 THE WITNESS: Yes, I do. 23 BY ATTORNEY DAVIES: 24 Q. And do you see one of the 25 formulations of the invention that is described as</p>
<p style="text-align: right;">Page 240</p> <p>1 inhalation in solid and liquid form? 2 A. I see it. 3 Q. So you understand this patent to be 4 describing the use of inhaled treprostinil in either 5 solid or liquid forms as a treatment? 6 ATTORNEY DYKHUIS: Objection to 7 form. Misstates. 8 THE WITNESS: Yes. 9 BY ATTORNEY DAVIES: 10 Q. Could you go to Example 4 on page 5 11 beginning with paragraph 61. 12 A. Okay. 13 Q. Here Example 4 refers to the effects 14 of treprostinil, either in the form of Remodulin or 15 inhaled, on patients analyzed using the six-minute 16 walk test. 17 Do you see that? 18 A. I do. 19 Q. And then it goes on to describe the 20 six-minute walk test as a standard assessment of 21 exercise capacity and breathlessness in patients 22 with lung disease. 23 Do you see that? 24 A. I do. 25 ATTORNEY DYKHUIS: Object to form.</p>	<p style="text-align: right;">Page 241</p> <p>1 THE WITNESS: I do. 2 BY ATTORNEY DAVIES: 3 Q. Do you agree with that statement? 4 ATTORNEY DYKHUIS: Object to form. 5 THE WITNESS: Yes. 6 BY ATTORNEY DAVIES: 7 Q. So this patent application describes 8 the assessment of inhaled treprostinil therapy using 9 a six-minute walk test as an assessment of exercise 10 capacity; correct? 11 ATTORNEY DYKHUIS: Object to form. 12 Mischaracterizes. 13 THE WITNESS: It appears to be so. 14 BY ATTORNEY DAVIES: 15 Q. Doctor, can you look at 16 Paragraph 82, which is Example 6 or the start of 17 Example 6, I should say. 18 A. Okay. 19 Q. Just let me know once you're there. 20 A. Yes. 21 Q. So here it's describing, "The 22 following study shows the vehicle of intravenous 23 treprostinil in patients with idiopathic pulmonary 24 fibrosis and pulmonary hypertension." 25 Do you see that?</p>

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1 A. I do.
2 Q. With that description in Paragraph
3 82, do you understand that this patent is, in fact,
4 directed to PH including PH-ILD?
5 ATTORNEY DYKHUIS: Object to form.
6 Form. Foundation. Speculative.
7 THE WITNESS: You know, I can't
8 answer that because these are just
9 examples. These are not specific claims,
10 as far as I can tell. These are just 19
11 examples in the literature. So there's
12 no specific claim here.
13 So if you look at this example,
14 it's intravenous treprostinil anyway.
15 Small segment of IPF for pulmonary
16 hypertension. I guess I don't know if
17 you're going to go to the claim, there's
18 a claim, and this is beyond my realm of
19 expertise in terms of how the patents are
20 formulated and what they cover.
21 But there's mention put in this of
22 many different things, and I'm not sure
23 just because they mention it you can
24 connect the dots in terms of what it
25 covers.

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1 you're there.
2 A. Yeah.
3 Q. And Paragraph 24 states, "Many acute
4 and chronic lung disorders with variable degrees of
5 inflammation and fibrosis are collectively referred
6 to as interstitial lung diseases. Because of the
7 stiff fibrosis of the lung, pulmonary or arterial
8 hypertension, PAH, is often a late complication of
9 some forms of ILD."
10 Do you see that?
11 A. I do.
12 Q. Do you understand that to be
13 describing PH-ILD?
14 ATTORNEY DYKHUIS: Object to form.
15 THE WITNESS: That actually
16 doesn't. It's describing PAH, which is
17 Group 1 pulmonary hypertension, and this
18 goes to what I mentioned earlier that
19 sometimes patients will develop what I
20 would regard as pulmonary hypertension
21 disproportionate to the extent of their
22 lung disease, in which case I would
23 regard them as having Group 1 pulmonary
24 arterial hypertension. So that's what I
25 mean.

1 BY ATTORNEY DAVIES:
2 Q. Can you go to Paragraph 50, Doctor,
3 and that's back on page 4. And it's right before
4 the Example section.
5 A. (Witness complies with request.)
6 Q. And Example 50 provides a
7 description of what the examples are. It states,
8 "The examples described herein are illustrative of
9 present invention and are not intended to be
10 limitations thereon."
11 Do you see that?
12 A. I do.
13 Q. So from what you understand the
14 examples in the patent to actually be illustrations
15 of the present inventions described in this patent?
16 ATTORNEY DYKHUIS: Object to form.
17 Foundation and calls for a legal
18 conclusion.
19 THE WITNESS: I think it's beyond
20 my expertise to comment on that.
21 BY ATTORNEY DAVIES:
22 Q. PH IPH is a form of PH-ILD; right?
23 A. Yes.
24 Q. If you go to Paragraph 24 of this
25 patent application description, let me know once

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1 BY ATTORNEY DAVIES:
2 Q. So if you have a patient with PAH as
3 well as ILD complications, you would not consider
4 that to be a PH-ILD patient. Is that correct?
5 ATTORNEY DYKHUIS: Objection to
6 form.
7 THE WITNESS: It goes down to
8 where are you going to group the patient.
9 And so to me, the way this reads is we're
10 talking about ILD complicated by
11 pulmonary hypertension or associated with
12 pulmonary hypertension that is severe
13 enough and out of proportion to the lung
14 disease to be regarded as Group 1 PAH.
15 Any time you say "PAH," that
16 defaults to Group 1. PH covers one to
17 five, but PAH is purely Group 1.
18 BY ATTORNEY DAVIES:
19 Q. Do other people in the field view
20 that distinction the same way as you, or is there a
21 difference in opinions as to that point as to
22 whether a patient with PAH and underlying ILD would
23 be a PH-ILD patient or not?
24 ATTORNEY DYKHUIS: Objection to
25 form. Speculation.

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1 THE WITNESS: I think anyone who
2 is familiar with the field of pulmonary
3 hypertension knows and recognizes that
4 distinction. You could catch someone who
5 is not. It's a common misconception
6 amongst people who go into pulmonary
7 hypertension to talk about PAH and PH
8 interchangeably, but not amongst people
9 who know pulmonary hypertension.

10 If you say "PAH," you're referring
11 to Group 1 pulmonary hypertension.

12 BY ATTORNEY DAVIES:

13 Q. Have you ever seen a patient in your
14 clinical practice who you would consider to have --
15 who you would consider to have been suffering from
16 both Group 1 PAH and Group 3 PH-ILD?

17 ATTORNEY DYKHUIS: Object to form.

18 THE WITNESS: No. That's a
19 theoretic concept that's impossible to
20 figure out. You either make the
21 distinction that that is more of a
22 Group 1 phenotype or this is Group 3.
23 You can't say there's, you know, a little
24 bit of three in some. It's impossible to
25 thread that needle.

1 BY ATTORNEY DAVIES:

2 Q. How do you decide where the dividing
3 line is between these patients?

4 A. That's a problem and one of a lot of
5 debate. There are cases that are clearly Group 3,
6 cases that are clearly Group 1, and there's a
7 spectrum between them. And I think I've alluded to
8 it earlier.

9 You look at the severity of the lung
10 disease in relation to the severity of the
11 hemodynamic impairment, and it becomes a subject of
12 judgment call where they best reside, Group 1 or
13 Group 3.

14 ATTORNEY DAVIES: Let's take a
15 break if that's okay.

16 (Discussion held off the
17 record.)

18 THE VIDEOGRAPHER: We are off the
19 record at 15:18.

20 (Recess taken from 3:18 p.m.
21 to 3:43 p.m.)

22 THE VIDEOGRAPHER: We are the
23 record at 15:43.

24 BY ATTORNEY DAVIES:

25 Q. Welcome back, Dr. Nathan. At any of

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1 the breaks today, did you have any discussions with
2 counsel about your testimony?

3 A. No.

4 ATTORNEY DAVIES: Okay. I have no
5 further questions, but obviously reserve
6 the right to follow-up based on what you
7 may or may not ask, Art.

8 EXAMINATION BY

9 ATTORNEY DYKHUIS:

10 Q. Dr. Nathan, I have a few questions
11 for you.

12 Understanding you have not been feeling all
13 that well today and wanted to clarify some of the
14 testimony after lunch.

15 Do you recall some questions about the '793
16 patent claims and then how, if at all, they relate
17 to improving exercise capacity?

18 ATTORNEY DAVIES: Objection.

19 Form.

20 THE WITNESS: I do.

21 BY ATTORNEY DYKHUIS:

22 Q. Let's get out, it's Exhibit 8 and 9.
23 You have a number in front of you. Find 8 and 9.

24 A. (Witness complies with request.)

25 Q. I think Exhibit 9 is the '327

1 patent; correct?

2 A. That's correct.

3 Q. Let's turn to the claim at the end
4 if you would, please.

5 A. Okay.

6 Q. Can you look at Claim 1.

7 A. Yes.

8 Q. And Claim 1 recites a method of
9 improving exercise capacity in a patient having
10 pulmonary hypertension associated with interstitial
11 lung disease.

12 Do you see that?

13 ATTORNEY DAVIES: Objection.
14 Form.

15 THE WITNESS: I do.

16 BY ATTORNEY DYKHUIS:

17 Q. So Claim 1 of the '327 patent
18 involves explicitly improving exercise capacity in
19 a patient having pulmonary hypertension associated
20 with interstitial lung disease?

21 A. Yes.

22 ATTORNEY DAVIES: Objection.

23 Form.

24 Q. Then if you can turn to the '793
25 patent, which is Exhibit 8.

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1 A. Okay.
2 Q. And let's go to the claims of the
3 '793 patent. Tell me when you've got those pulled
4 up.
5 A. I'm here.
6 Q. Does Claim 1 of the '793 patent
7 say -- have any words about improving exercise
8 capacity?
9 A. No, it does not.
10 Q. Let's keep those two handy, but then
11 your declaration is Exhibit 2. And then let's go
12 to Paragraph 176, please.
13 A. Yes. I'm at 176.
14 Q. Did counsel direct you specifically
15 to Paragraph 176 at all today?
16 ATTORNEY DAVIES: Objection.
17 Form.
18 THE WITNESS: No.
19 BY ATTORNEY DAVIES:
20 Q. Could you read 176 just to yourself
21 and let me know when you're finished.
22 ATTORNEY DAVIES: Same objection.
23 THE WITNESS: I remember now
24 opining on this, that the '793 patent
25 does not teach anything about what the

1 '327 patent has as its claim in terms of
2 improving exercise tolerance, FVC and
3 other things that are within the -327
4 claim.
5 BY ATTORNEY DYKHUIS:
6 Q. So why is it your opinion that the
7 '793 patent doesn't teach anything about the '327
8 patent improving exercise capacity?
9 ATTORNEY DAVIES: Objection.
10 Form.
11 THE WITNESS: There are a lot of
12 examples thrown within it. I'm sorry.
13 This is -- I was getting my patents
14 confused. Let me start again.
15 The '793 patent, all that does is
16 it talks about treating pulmonary
17 hypertension. And treating pulmonary
18 hypertension means taking pressures that
19 are high within the lungs and making them
20 lower.
21 There's no mention of any kind of
22 clinical benefit in the original '793
23 patent, and that's what the '327 patent
24 gets into.
25

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1 BY ATTORNEY DYKHUIS:
2 Q. Okay. You can close your
3 declaration there. And then you still have the
4 '327 and '793 patent in front of you, Doctor?
5 A. '793 and '327, yes.
6 Q. Which one do you have on the left?
7 A. This is the '793.
8 Q. Could you open that '793 back to the
9 claims again.
10 A. (Witness complies with request.)
11 Okay.
12 Q. And I'd like to do a little
13 side-by-side there. You can hold it if you like.
14 I actually want to ask you about a specific
15 question again in a moment.
16 A. Okay.
17 Q. So you were asked a question
18 earlier, and I'm just going to read it.
19 "Do you believe that Claim 1 of the '793
20 patent also includes a method of improving exercise
21 capacity in a patient having pulmonary hypertension
22 associated with interstitial lung disease?"
23 There was an objection, and then you said,
24 "That's what it says."
25 Do you recall that question and answer from

1 earlier today?
2 A. I don't recall specifically, but I
3 told you wrong. I think that I was thinking about
4 the '327 patent when that question was posed at me.
5 So I apologize for getting the numbers confused.
6 Clearly it does, which the '793 patent does not
7 mention anything about improving exercise capacity,
8 so that was not -- my mistake.
9 Q. So when you said "That's what it
10 says," you were referring to the '327 patent?
11 ATTORNEY DAVIES: Objection.
12 Form.
13 You can answer.
14 THE WITNESS: Yes, that's correct.
15 BY ATTORNEY DYKHUIS:
16 Q. I think on the left you have the
17 '793 patent. Let's look at the cover page.
18 You were asked some questions earlier today
19 about -- I think it was a conference of some sort
20 where you were admonished publically over the
21 RISE-IIP study?
22 A. That's correct.
23 Q. That was something that was in front
24 of 500 people or so?
25 A. Yes.

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1 Q. Who was it who was admonishing you?
2 A. It was Dr. Lewis Rubin.
3 Q. So on the cover of the '793 patent,
4 do you see a section Inventors, and it lists a few
5 people?
6 A. Yes.
7 Q. One of the inventors is Lewis J.
8 Rubin?
9 A. Yes, indeed. It's the same person.
10 ATTORNEY DYKHUIS: No further
11 questions.
12 EXAMINATION BY
13 ATTORNEY DAVIES::
14 Q. Just a couple additional questions
15 for me, Doctor.
16 If you look back at the '793 patent at
17 Claim 1, just let me know once you're there.
18 A. I'm there.
19 Q. Okay. So is it your opinion that
20 Claim 1 of the '793 patent excludes a method of
21 improving exercise capacity in a patient with
22 PH-ILD?
23 ATTORNEY DYKHUIS: Object to form.
24 Foundation.
25 THE WITNESS: Yes, it does.

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1 ATTORNEY DYKHUIS: No further
2 questions for UTC.
3 THE VIDEOGRAPHER: We are off the
4 record at 15:54.
5 (Proceedings adjourned at
6 3:54 p.m.)
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1 BY ATTORNEY DAVIES:
2 Q. Counsel directed you to
3 paragraph 176 of your declaration. Do you recall
4 that?
5 A. I don't recall that.
6 Q. Can you go to paragraph 176 of your
7 declaration.
8 A. Okay.
9 Q. Did you prepare paragraph 176 in
10 your declaration, or was that prepared by counsel?
11 ATTORNEY DYKHUIS: Objection to
12 form.
13 THE WITNESS: To be honest, I
14 don't recall. We all had a hand in this
15 declaration, and I don't recall who had
16 the original version. It might have been
17 counsel. There were many iterations
18 going backwards and forwards. So I can't
19 a hundred percent attest to that.
20 I certainly had a role in this in
21 terms of editing, adding, and deleting
22 things that I didn't think was necessary
23 to make it my own words.
24 ATTORNEY DAVIES: We have no
25 further questions at this time.

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1 DISTRICT OF COLUMBIA: SS
2 I, Barbara Moore, a Registered Court Reporter
3 of the District of Columbia, do hereby certify that
4 these proceedings took place before me at the time
5 and place herein set out, and the proceedings were
6 recorded stenographically by me and this transcript
7 is a true record of the proceedings.
8
9 I further certify that I am not of counsel to
10 any of the parties, nor an employee of counsel nor
11 related to any of the parties, nor in any way
12 interested in the outcome of this action.
13
14
15
16
17 BARBARA MOORE, CRR, RMR
18
19
20 My Commission Expires:
21 September 30, 2028
22
23
24
25

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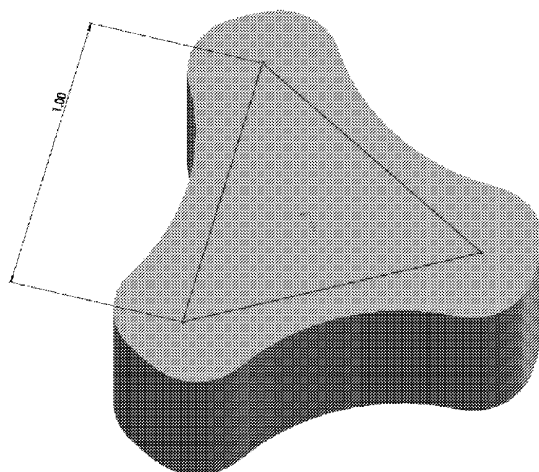
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(54) Title: DRY POWDER TREPROSTINIL FOR THE TREATMENT OF PULMONARY HYPERTENSION

FIGURE 1



1 micrometer 'pollen' particle

(57) Abstract: A dry powder inhalation treatment for pulmonary
arterial hypertension includes a dose of dry particles comprising
greater than 25 micrograms of treprostinil enclosed in a capsule.
The dry particles can include treprostinil, a wetting agent, a hy-
drophobicity modifying agent, a pH modifying agent and a buffer.
A method of treating a patient having pulmonary arterial hyperten-
sion includes providing a patient a dry powder inhaler, providing
the patient at least one capsule for use in the dry powder inhaler, the
capsule including at least 25 micrograms of treprostinil.

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Dry Powder Treprostinil for the Treatment of Pulmonary Hypertension

Cross-Reference to Related Applications

[0001] This application claims priority to and the benefit of U.S. Provisional Patent Application No. 62/332,013, filed May 5, 2016, U.S. Provisional Patent Application No. 62/404,960, filed October 6, 2016, U.S. Provisional Patent Application No. 62/440,078, filed December 29, 2016, and U.S. Provisional Patent Application No. 62/472,204, filed March 16, 2017, all of which are incorporated herein by reference in their entireties.

TECHNICAL FIELD

[0002] The present invention provides an improvement to the treatment of pulmonary hypertension, a condition that deteriorates the lives of many thousands of patients toward an untimely death. The present invention provides, for the first time, a stable, user friendly, uniform dry powder inhaled treprostinil formulation, methods of making, and use thereof in humans.

BACKGROUND

[0003] Pulmonary arterial hypertension (PAH) is a complex, multifactorial, progressive, and life-threatening disease characterized by proliferative and obstructive changes in the pulmonary vasculature and involving numerous biochemical pathways and cell types. The disease is characterized by elevated pulmonary arterial pressure caused by narrowing of the blood vessels in the lungs and, ultimately, right ventricular failure. The disease carries a poor prognosis associated with significant morbidity and mortality, having a historical survival rate less than five years. PAH is a sub-group of pulmonary hypertension (PH), which is elevation of blood pressure in lungs. Endothelial dysfunction is thought to occur early on, leading to cell proliferation and structural changes in the pulmonary vasculature that lead to increased pulmonary arterial pressure (PAP) and resultant right ventricular enlargement and dysfunction. In addition, endothelial dysfunction results in chronically impaired production of vasoactive mediators, such as nitric oxide (NO) and prostacyclin, along with prolonged overexpression of vasoconstrictors, such as endothelin-1.

[0004] PAH affects approximately 15 out of every one million individuals. There are approximately 1,000 new cases of PAH diagnosed in the United States each year. The mean age

at diagnosis is between 50 and 65 years of age, although the disorder may present much earlier in childhood or even infancy. While gender-based prevalence estimates for PAH are variable, estimates for the overall prevalence of pulmonary hypertension (PH) in females is approximately twice that of males.

[0005] PAH is part of a larger classification for pulmonary hypertension which is divided into five groups based on World Health Organization (WHO) criteria (designated as WHO Groups 1 through 5). PAH is used to describe exclusively WHO Group 1. Pulmonary hypertension is used to describe the remaining four groups (WHO Groups 2-5) and also when referring to all 5 groups collectively.

- WHO Group 1 - PAH: Pulmonary arterial hypertension.
- WHO Group 2 - PH: Pulmonary hypertension secondary to left heart disease.
- WHO Group 3 - PH: Pulmonary hypertension secondary to lung diseases or hypoxemia.
- WHO Group 4 - PH: Chronic thromboembolic pulmonary hypertension.
- WHO Group 5 - PH: Pulmonary hypertension with unknown mechanisms.

[0006] PAH initially presents as exertional dyspnea, lethargy, and fatigue and is often confused for other disease states. As PAH progresses and right ventricular failure develops, exertional chest pain (i.e., angina), exertional syncope, and peripheral edema may develop. Following confirmation of diagnosis based on hemodynamic parameters, treatment is recommended to lower pulmonary pressures and treat the symptoms of PAH. Although no cure exists for PAH, treatment of PAH is directed at improving hemodynamic measures, New York Heart Association (NYHA) functional class, the 6 minute walk distance (6MWD), quality of life, and, in some studies, survival.

[0007] The severity of PAH may be classified according to the NYHA heart failure guidelines as follows:

- NYHA Class I: Patients with no limitation of activities; they suffer no symptoms from ordinary activities.
- NYHA Class II: Patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.

- NYHA Class III: Patients with marked limitation of activity; they are only comfortable at rest.
- NYHA Class IV: Patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

[0008] While the exact underlying cause of PAH is unclear, mutations in the bone morphogenic protein receptor type II (BMP2) gene account for approximately 75% of familial PAH and up to 25% of apparently sporadic PAH cases. These mutations may promote cell division or prevent cell death, resulting in an overgrowth of cells in smaller pulmonary arteries. This overgrowth increases resistance to blood flow, triggering hypertension. Additional genetic abnormalities may also contribute to PAH.

[0009] Currently Available Treatments

[0010] There are five classes of drugs that have been approved to treat PAH, including endothelin receptor antagonists (ERAs), phosphodiesterase type 5 (PDE5) inhibitors, soluble guanylate cyclase stimulators, prostacyclin receptor agonists, and prostacyclin analogs. Approved PAH therapies and their route of administration include:

- ERA: bosentan (oral) and ambrisentan (oral)
- PDE5: sildenafil (oral, intravenous (IV) and tadalafil (oral)
- Soluble Guanylate Cyclase (sGC) Stimulator: riociguat (oral)
- Prostacyclin Receptor Agonist: selexipag (oral)
- Prostacyclin Analog: epoprostenol (IV) iloprost (inhaled), and treprostinil (oral), (subcutaneous and IV), and (inhaled)

[0011] Treprostinil is a chemically stable tricyclic benzidine prostanoid with vasodilator properties that is capable of reducing pulmonary vasoconstriction with minimal effects on systemic blood pressure. Treprostinil has been approved for the treatment of PAH under the trade names REMODULIN[®] (United Therapeutics Corporation; subcutaneous or IV infusion) and TYVASO[®] (United Therapeutics Corporation; inhaled via ultrasonic, pulsed nebulization delivery device). While both have proven effective for PAH, one advantage of TYVASO's

inhaled route of administration is that it brings the drug very near the desired site of action (pulmonary arteries in the lungs).

[0012] Despite the current treatment options for PAH patients, each option includes drawbacks, most notably for the inhaled route of administration Tyvaso requires use of a large, cumbersome nebulization device that requires power, water and user manipulation for cleaning and operating. Moreover, the nebulization device by its nature is not convenient to the patient as compared to carrying a small, concealable dry powder inhalation device such as those used for treating asthma and many other chronic and acute issues. Furthermore, nebulized treprostinil has shown clinical limitations on treprostinil dosing, which may limit the applicability of the inhaled route of administration to a smaller subsector of PAH patients than necessarily treatable via the inhaled route from a dry powder inhaled treprostinil product of the present invention.

SUMMARY OF THE INVENTION

[0013] The present inventors have developed and reduced to practice an inhalation dry powder formulation of treprostinil that is produced using Liquidia's PRINT[®] Technology (Particle Replication in Nonwetting Templates), LIQUIDIA TECHNOLOGIES, INC. This PRINT particle formulation for dry powder delivery of treprostinil (otherwise referred to as LIQ861) is under clinical evaluation. The present applicants intend to use the same indication (i.e., treatment of pulmonary arterial hypertension [WHO Group 1] in patients with NYHA Class III symptoms, to improve exercise ability) dose and dose regimen (4X/day) as defined in the approved nebulized treatment label (TYVASO[®] UNITED THERAPEUTICS). In particular, the present invention provides for dosing levels that exceed the maximum tolerated dose delivered through a nebulizer. In some cases the present invention may also treat other indications under the pulmonary hypertension disease states.

[0014] In some embodiments, a dry powder inhalation treatment for pulmonary arterial hypertension according to the present invention includes a dose of dry particles comprising greater than 25 micrograms of treprostinil enclosed in a capsule. In some embodiments, the dose of dry particles comprises from about 25 micrograms to about 400 micrograms of treprostinil. In some embodiments, the dose of dry particles comprises from about 50 micrograms to about 350 micrograms of treprostinil. In some embodiments, the dose of dry

particles comprises from about 75 micrograms to about 300 micrograms of treprostinil. In some embodiments, the dose of dry particles comprises from about 100 micrograms to about 300 micrograms of treprostinil. In some embodiments, the dose of dry particles includes greater than or equal to 100 micrograms of treprostinil. In some embodiments, the dose of dry particles comprises greater than or equal to 150 micrograms of treprostinil. In some embodiments, the dose of dry particles comprises greater than or equal to 200 micrograms of treprostinil. In some embodiments, the dose of dry particles comprises greater than or equal to 250 micrograms of treprostinil. In some embodiments, the dose of dry particles comprises greater than or equal to 300 micrograms of treprostinil. In some embodiments, the dose of dry particles includes greater than or equal to 5 mg of the dry particles. In some embodiments, the dose of dry particles includes greater than or equal to 10 mg of the dry particles. In yet other embodiments, the dose of dry particles includes greater than or equal to 15 mg of the dry particles. In further embodiments, a dry powder treatment for pulmonary arterial hypertension, includes a single capsule enclosing 5 mg or more dry particles comprising 25 micrograms of treprostinil per each 5 mg of the dry particles.

[0015] In some embodiments, a method of treating a patient having pulmonary arterial hypertension includes providing a patient a dry powder inhaler, providing the patient at least one capsule for use in the dry powder inhaler, wherein the capsule comprises at least 25 micrograms of treprostinil, and instructing the patient to utilize the dry powder inhaler to inhale the treprostinil. In some such embodiments, the capsule includes at least 50 micrograms of treprostinil. In some embodiments, the capsule includes at least 100 micrograms of treprostinil. In some embodiments, the capsule comprises at least 150 micrograms of treprostinil. In some embodiments, the capsule comprises greater than or equal to 200 micrograms of treprostinil. In some embodiments, the capsule comprises greater than or equal to 250 micrograms of treprostinil. In some embodiments, the capsule comprises greater than or equal to 300 micrograms of treprostinil. In some embodiments, the capsule comprises from about 25 micrograms to about 400 micrograms of treprostinil. In some embodiments, the capsule comprises from about 50 micrograms to about 350 micrograms of treprostinil. In some embodiments, the capsule comprises from about 75 micrograms to about 300 micrograms of treprostinil. In some embodiments, the capsule comprises from about 100 micrograms to about 300 micrograms of treprostinil. In further embodiments, the patient may be prescribed to use

two capsules per dose cycle per day, generally with PAH requiring 4 times per day dosing. In some embodiments, the patient may be prescribed to use three capsules per day. In some embodiments, the patient may be prescribed to use four capsules per day. In some embodiments, a method of treating a patient having pulmonary arterial hypertension includes dosing the patient having pulmonary arterial hypertension with a dry powder dose of treprostinil, wherein the dose of treprostinil is greater than 85 micrograms (e.g., about 100 micrograms to about 350 micrograms). In some embodiments, the patient may be dosed one, two, three, four, or more times per day. A further method of treating a patient having pulmonary arterial hypertension includes delivering, in dry powder, greater than 12.5 micrograms of treprostinil to a patient per breath. In another embodiment, a method of treating a patient having pulmonary arterial hypertension includes delivering, in dry powder, greater than 25 micrograms of treprostinil to a patient per breath. In another embodiment, a method of treating a patient having pulmonary arterial hypertension includes delivering, in dry powder, from about 12.5 to about 50 micrograms of treprostinil to a patient per breath. In yet another embodiment, a method of treating a patient having pulmonary arterial hypertension includes delivering, in dry powder, about 25 to about 50 micrograms of treprostinil to a patient per breath. In a further embodiment, a method of treating a patient having pulmonary arterial hypertension includes delivering, in dry powder, greater than 50 micrograms of treprostinil to a patient per breath. In a further embodiment, a method of treating a patient having pulmonary arterial hypertension includes delivering, in dry powder, greater than or equal to 100 micrograms of treprostinil to a patient per breath. In a further embodiment, a method of treating a patient having pulmonary arterial hypertension includes delivering, in dry powder, greater than or equal to 150 micrograms of treprostinil to a patient per breath. In a further embodiment, a method of treating a patient having pulmonary arterial hypertension includes delivering, in dry powder, greater than or equal to 200 micrograms of treprostinil to a patient per breath.

[0016] A dry powder inhalation composition for treating pulmonary arterial hypertension according to a further embodiment includes a plurality of dry powder particles comprising treprostinil, a non-reducing sugar, a wetting agent, a hydrophobicity modifying agent, a pH modifying agent and a buffer. In some such embodiments, the bulking agent comprises trehalose dihydrate. In some embodiments, the wetting agent comprises polysorbate 80. In some embodiments, the hydrophobicity modifying agent comprises L-leucine. In some

embodiments, the pH modifying agent comprises sodium citrate dihydrate. In some embodiments, the buffer comprises sodium chloride. In certain embodiments, the composition comprises less than about 4 percent by weight water. In some embodiments, the composition comprises less than about 2 percent by weight water. In some embodiments, the composition comprises less than about 1 percent by weight water.

[0017] In yet further embodiments, the dry powder particles include particles having a three dimensional shape including a width and length not less than 1 micrometer and not more than 2 micrometers and a depth not less than 0.3 micrometers and not more than 0.8 micrometers. In some embodiments, the dry powder particles comprise a dried solution comprising trehalose dihydrate, L-leucine, treprostinil sodium, polysorbate 80, sodium citrate dihydrate, sodium chloride and water. In some embodiments, the dry powder particles comprise by percent solids about 0.581 percent treprostinil sodium, about 92.32 percent trehalose, about 2.19 percent polysorbate 80, about 4.39 percent L-leucine, about 0.26 percent sodium citrate, and about 0.25 percent sodium chloride.

[0018] A method of making a particle for dry powder delivery to the lung of a patient in need thereof, in some embodiments, includes molding a composition comprising about 12.30 weight percent trehalose dihydrate, about 0.53 weight percent L-leucine, about 0.07 weight percent treprostinil sodium, about 0.26 weight percent polysorbate 80, about 0.04 weight percent sodium citrate dihydrate, about 0.03 weight percent sodium chloride and about 86.78 weight percent water into a particle. In some embodiments, the method of making the particle further includes drying the composition such that the particle comprises less than 4 percent by weight water.

BRIEF DESCRIPTION OF THE FIGURES

[0019] The foregoing summary, as well as the following detailed description of the invention, will be better understood when read in conjunction with the appended drawings. For the purpose of illustrating the invention, there are shown in the drawings embodiments which are presently preferred. It should be understood, however, that the invention can be embodied in different forms and thus should not be construed as being limited to the illustrated embodiments set forth herein.

[0020] Figure 1 shows a three-dimension rendering of a pollen particle according to an embodiment of the present invention.

[0021] Figure 2 shows an example NGI distribution for active particles (PAH-1R-0943-010). For each of the three data sets represented for each collection cup, the beginning of the run is the left hand bar (A1), the middle of the run is the center bar (B1), and the end of the run is the right hand bar (C1). Data was obtained using the Monodose Model 8 device (95 L/min, 2 sec).

[0022] Figures 3A and 3B are tables including data for Cohort 1 of a clinical trial. The table shown in Figure 3A contains a summary of the treprostinil concentration-time data for individual subjects with descriptive statistics for the six active subjects in Cohort 1. Preliminary non-compartmental PK parameters for treprostinil are summarized in the table shown in Figure 3B.

[0023] Figures 4A and 4B are tables including data for Cohort 2 of a clinical trial. The table shown in Figure 4A contains a summary of the treprostinil concentration-time data for individual subjects with descriptive statistics for the six active subjects in Cohort 2. Preliminary non-compartmental PK parameters for treprostinil for Cohort 2 are summarized in the table shown in Figure 4B.

[0024] Figures 5A and 5B are tables including data for Cohort 3 of a clinical trial. The table shown in Figure 5A contains a summary of the treprostinil concentration-time data for individual subjects with descriptive statistics for the six active subjects in Cohort 3. Preliminary non-compartmental PK parameters for treprostinil for Cohort 3 are summarized in the table shown in Figure 5B.

[0025] Figures 6A and 6B are tables including data for Cohort 4 of a clinical trial. The table shown in Figure 6A contains a summary of the treprostinil concentration-time data for individual subjects with descriptive statistics for the six active subjects in Cohort 4. Preliminary non-compartmental PK parameters for treprostinil for Cohort 4 are summarized in Figure 6B.

[0026] Figures 7A and 7B are tables including data for Cohort 5 for a clinical trial. The table shown in Figure 7A contains a summary of the treprostinil concentration-time data for individual subjects with descriptive statistics for the six active subjects in Cohort 5. Preliminary non-compartmental PK parameters for treprostinil for Cohort 5 are summarized in Figure 7B.

[0027] Figures 8A, 8B, and 8C are tables including data for Cohort 6 for a clinical trial. The table shown in Figure 8A contains a summary of the treprostinil concentration-time data for individual subjects with descriptive statistics for the six active subjects in Cohort 6-R. Preliminary non-compartmental PK parameters for treprostinil for Cohort 6-R are summarized in Figure 8B. Preliminary non-compartmental PK parameters for treprostinil for Cohort 6-Original are summarized in Figure 8C.

[0028] Figures 8D, 8E, 8F, and 8G contain data for the clinical trial. Mean concentration-time data for each of the six cohorts is displayed on a linear scale in Figure 8D. Plots of the relationship between dose and C_{max} and AUC_{inf} are displayed in Figure 8E and Figure 8F, respectively. A plot of the relationship between dose and the oral clearance, CL/F, is shown in Figure 8G.

[0029] Figure 9 is an SEM image showing pollen-shaped particles according to an embodiment of the present invention.

[0030] Figure 10 is a flow diagram showing a process of manufacturing particles according to an embodiment of the present invention.

[0031] Figure 11 shows an example dry powder inhalation device which may be used to deliver particles to a patient in accordance with embodiments of the present invention.

DETAILED DESCRIPTION OF EMBODIMENTS

[0032] Drug Substance

[0033] The drug substance (DS) according to embodiments of the present invention is treprostinil, which is a synthetic analog of prostacyclin (PGI₂). The IUPAC name for treprostinil is (2-[[[(1R,2R,3aS,9aS)-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-2,3,3a,4,9,9a-hexahydro-1H-cyclopenta[g]naphthalen-5-yl]oxy]acetic acid).

[0034] Inhalation Powder Drug Product

[0035] The inhalation powder drug product according to certain aspects of the present invention provides a dry powder dosage form of treprostinil and excipients formed into a particle

(drug product intermediate, or DP-intermediate) that is, in some embodiments, filled into a capsule, for example, a hydroxypropyl methylcellulose (HPMC) capsule (size 3) (LIQ861). In some embodiments, the DP-intermediate is a treprostinil/excipient matrix from which particles of precise size and shape are formed according to the methods herein. In one example, the particles of the DP-intermediate comprise a shape corresponding generally to a rounded triangular shape having a volume, where the inner portion of the rounded triangular shape, in size, fits a 1 micrometer equilateral triangle (otherwise referred to as being pollen-shaped). A three-dimensional rendering of such a particle shape is depicted in Figure 1. In another embodiment, the pollen-shape may be trefoil-shaped with an inscribed circle diameter of 1 micrometer, and a prescribed thickness of a value or range between 0.5 and 1 micrometer, or more preferred 0.7 micrometer. In addition, certain embodiments of the present drug product includes particles having 0.5% treprostinil used in a first clinical study to investigate dose levels of 25 mcg, 50 mcg, 75 mcg, 100 mcg, 125 mcg and 150 mcg treprostinil in LIQ861. In further embodiments, a drug product according to the present invention may provide dose levels of 175 mcg, 200 mcg, 225 mcg, 250 mcg, 275 mcg, 300 mcg, 325 mcg, or 350 mcg treprostinil. In further embodiments, a drug product according to the present invention may provide dose levels of 50 mcg treprostinil plus or minus 10 mcg, 9 mcg, 8 mcg, 7 mcg, 6 mcg, 5 mcg, 4 mcg, 3 mcg, 2 mcg or 1 mcg treprostinil loaded into capsules for delivery to a patient in a dry powder. In further embodiments, a drug product according to the present invention may provide dose levels of 75 mcg treprostinil plus or minus 10 mcg, 9 mcg, 8 mcg, 7 mcg, 6 mcg, 5 mcg, 4 mcg, 3 mcg, 2 mcg or 1 mcg treprostinil loaded into capsules for delivery to a patient in a dry powder. In further embodiments, a drug product according to the present invention may provide dose levels of 100 mcg treprostinil plus or minus 10 mcg, 9 mcg, 8 mcg, 7 mcg, 6 mcg, 5 mcg, 4 mcg, 3 mcg, 2 mcg or 1 mcg treprostinil loaded into capsules for delivery to a patient in a dry powder. In further embodiments, a drug product according to the present invention may provide dose levels of 150 mcg treprostinil plus or minus 10 %, 9 %, 8 %, 7 %, 6 %, 5 %, 4 %, 3 %, 2 % or 1 % treprostinil loaded into capsules for delivery to a patient in a dry powder. In further embodiments, a drug product according to the present invention may provide dose levels of 200 mcg treprostinil plus or minus 10 %, 9 %, 8 %, 7 %, 6 %, 5 %, 4 %, 3 %, 2 % or 1 % mcg treprostinil loaded into capsules for delivery to a patient in a dry powder. In further embodiments, a drug product according to the present invention may provide dose levels of 300

mcg treprostinil plus or minus 10 %, 9 %, 8 %, 7 %, 6 %, 5 %, 4 %, 3 %, 2 % or 1 % treprostinil loaded into capsules for delivery to a patient in a dry powder.

[0036] According to the present invention, due to the formulation of the present dry powder particles, the particles remain stable for long periods of time at relatively low humidity conditions. In some embodiments, the present invention provides dry powder particles packaged under sealed conditions that remain stable for more than 3 months at 40 degrees Celsius at 75 percent relative humidity. Therefore, the particles can be utilized to provide a patient with a dry powder inhaled drug form of treprostinil, not previously available until the present invention. This invention, in some embodiments, provides a user with a reduction in interaction with drug product by removing the requirements on the patient to reconstitute their drug product for use in a nebulizer device. The patient is also enabled to receive equal dosing with more than 50 percent reduction in breath treatments on a device, and in some embodiments more than 65 percent reduction in breath treatments.

[0037] The present invention, in some embodiments, also provides a dry formulation of treprostinil, which upon delivery to a patient via the inhaled route, becomes soluble and pharmaceutically available in less than 10 seconds. In some embodiments, the dry formulation composition becomes soluble and pharmaceutically available in less than 5 seconds. In some embodiments, the dry formulation composition becomes soluble and pharmaceutically available in less than 2 seconds. In some embodiments, the dry formulation composition becomes soluble and pharmaceutically available in about 1 second. In some embodiments, the dry formulation composition becomes soluble and pharmaceutically available in less than 1 second. In some embodiments, the dry formulation composition becomes soluble and pharmaceutically available in less than about 0.5 seconds. Furthermore, the excipients in the dry particle formulation of the present invention maintain pH and salt gradient during processing such that the active agent remains in a state to become soluble in the lung conditions of a user.

[0038] A detailed description of the LIQ861 formulation, particle composition, particle geometry, packaging, device, delivery, stability, dose, and a description of the use follows.

[0039] In some embodiments, a formulation according to the present invention includes a drug substance (e.g., Treprostinil, Treprostinil Sodium) together with one or more excipients. In some

embodiments, the one or more excipients may include a bulking agent, a wetting agent, a hydrophobicity modifier, a pH modifier, a buffer component, or combinations thereof. Examples of such formulations according to certain specific embodiments are provided in the tables below.

LIQ861 Drug Product-Intermediate Description for Active (LIQ861) and Placebo Formulations (dihydrate form calculations)

Component	Function	Quantity (mg/g) (Active)	Percent Solids
Treprostinil Sodium	Drug Substance	5.3 (5.0 as treprostinil)	0.53
Trehalose Dihydrate	Bulking Agent	930	92.97
Polysorbate 80	Wetting Agent	20	2.00
L-Leucine	Hydrophobicity Modifier	40	4.00
Sodium Citrate Dihydrate	pH Modifier	2.7	0.27
Sodium Chloride	Buffer Component	2.3	0.23

LIQ861 Drug Product-Intermediate Description for Active (LIQ861) and Placebo Formulations (anhydrous form calculations)

Component	Function	Quantity (mg/g) (Active)	Percent Solids	Normalized mg/g
Treprostinil Sodium	Drug Substance	5.3 (5.0 as treprostinil)	0.581	5.81
Trehalose	Bulking Agent	841	92.32	923.23
Polysorbate 80	Wetting Agent	20	2.19	21.94
L-Leucine	Hydrophobicity Modifier	40	4.39	43.89
Sodium Citrate	pH Modifier	2.4	0.26	2.60
Sodium Chloride	Buffer Component	2.3	0.25	2.52

[0040] Inhalation Device

[0041] According to an embodiment of administering the present invention drug particle, LIQ861 is administered using an RS00 Model 8 dry powder inhalation device (Plastiaple S.p.A.). The present invention provides for multi-day administration of LIQ861 according to some embodiments.

[0042] Indication

[0043] The present invention, according to an embodiment, is useful for the treatment of pulmonary arterial hypertension (WHO Group 1) in patients with NYHA Class III symptoms, to improve exercise ability.

[0044] Chemistry, Manufacturing, and Controls (CMC)

[0045] Drug Substance (DS)

[0046] The drug substance according to embodiments of the present invention is treprostinil and the salt form used for LIQ861 is treprostinil sodium. Detailed information about treprostinil sodium, including physical and chemical properties, characterization, manufacturing and controls, container closure system, and stability attributes may be found in the Drug Master File (DMF) lodged with the FDA for treprostinil. General information on the DS is provided herein.

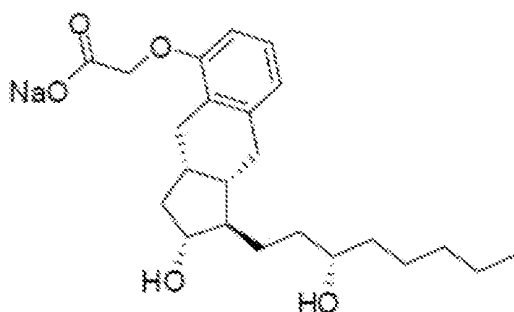
[0047] **Nomenclature**

[0048] The international non-proprietary name (INN) for LIQ861 is treprostinil sodium. The chemical name is 2-((1R,2R,3aS,9aS)-2-hydroxy-1-((S)-3-hydroxyoctyl)-2,3,3a,4,9,9a-hexahydro-1H-cyclopenta[b]naphthalen-5-yloxy)acetic acid, sodium salt. The chemical abstracts service registration number is [289480-64-4].

[0049] **Structure**

[0050] The structure of treprostinil sodium is depicted herein below. The molecular formula is $C_{23}H_{33}NaO_5$ and it has a molecular weight of 412.49 daltons.

[0051] **Chemical Structure of Treprostinil Sodium**



[0052] **General Properties**

[0053] Treprostinil sodium appears as a white or pale yellowish powder. It is very soluble in water and ethanol, very slightly soluble in acetone, and practically insoluble in acetonitrile, n-hexane, and ethyl acetate. The specific optical rotation calculated with reference to the anhydrous and solvent free basis is $[\alpha]_D^{20} = +38.0^\circ \sim +44.0^\circ$. It is hygroscopic. The pKa of treprostinil is 4.5, using aqueous titration with 20% ethanol as a co-solvent. The distribution

coefficient of treprostinil in various buffer solutions at various pH levels indicates distribution into octanol layers at all pH levels.

[0054] Inhalation Particle Drug Product – LIQ861

[0055] Description and Composition of the Drug Product Particle

[0056] The inhalation drug particle product, in some embodiments, includes or consists of a dry powder dosage form of treprostinil and excipients (drug product-intermediate; DP-intermediate; or drug particle) that may be filled into, for example, a HPMC capsule (size 3). The DP-intermediate, in some embodiments, is a treprostinil/excipient matrix from which particles of precise size (e.g., 1 μm) and shape (e.g., “pollen-shaped”) are created using Liquidia’s PRINT Technology. The “pollen-shaped” particles may also be described as trefoil-shaped, with an inscribed circle diameter of 1 μm , and a thickness of 0.7 μm . A three-dimensional rendering of such a particle shape is depicted in Figure 1. LIQ861 comprised drug product capsule strengths of 25 mcg, 50 mcg, and 75 mcg treprostinil used in the first clinical study to investigate planned dose levels of 25 mcg, 50 mcg, 75 mcg, 100 mcg, 125 mcg and 150 mcg treprostinil. The 100 mcg, 125 mcg and 150 mcg doses may be made up of a combination of lower dose capsules. In further embodiments, a drug product according to the present invention may provide capsules with dose levels of 175 mcg, 200 mcg, 225 mcg, 250 mcg, 275 mcg, 300 mcg, 325 mcg, or 350 mcg treprostinil. In further embodiments, a drug product according to the present invention may provide capsules with dose levels of 50 mcg treprostinil plus or minus 10 mcg, 9 mcg, 8 mcg, 7 mcg, 6 mcg, 5 mcg, 4 mcg, 3 mcg, 2 mcg or 1 mcg treprostinil for delivery to a patient in a dry powder. In further embodiments, a drug product according to the present invention may provide capsules with dose levels of 75 mcg treprostinil plus or minus 10 mcg, 9 mcg, 8 mcg, 7 mcg, 6 mcg, 5 mcg, 4 mcg, 3 mcg, 2 mcg or 1 mcg treprostinil for delivery to a patient in a dry powder. In further embodiments, a drug product according to the present invention may provide capsules with dose levels of 100 mcg treprostinil plus or minus 10 mcg, 9 mcg, 8 mcg, 7 mcg, 6 mcg, 5 mcg, 4 mcg, 3 mcg, 2 mcg or 1 mcg treprostinil for delivery to a patient in a dry powder. In further embodiments, a drug product according to the present invention may provide capsules with dose levels of 150 mcg treprostinil plus or minus 10 %, 9 %, 8 %, 7 %, 6 %, 5 %, 4 %, 3 %, 2 % or 1 % treprostinil for delivery to a

patient in a dry powder. In further embodiments, a drug product according to the present invention may provide capsules with dose levels of 200 mcg treprostinil plus or minus 10 %, 9 %, 8 %, 7 %, 6 %, 5 %, 4 %, 3 %, 2 % or 1 % mcg treprostinil for delivery to a patient in a dry powder. In further embodiments, a drug product according to the present invention may provide capsules with dose levels of 300 mcg treprostinil plus or minus 10 %, 9 %, 8 %, 7 %, 6 %, 5 %, 4 %, 3 %, 2 % or 1 % treprostinil for delivery to a patient in a dry powder. A summary of the LIQ861 formulation, including powder composition, particle geometry, and a description of the dosing unit according to certain exemplary embodiments follows.

LIQ861 Drug Product-Intermediate Description for Active (LIQ861) and Placebo Formulations (dihydrate)

Component	Function	Quantity (mg/g) (Active)	Percent Solids
Treprostinil Sodium	Drug Substance	5.3 (5.0 as treprostinil)	0.53
Trehalose Dihydrate	Bulking Agent	930	92.97
Polysorbate 80	Wetting Agent/Process Aide	20	20
L-Leucine	Hydrophobicity Modifier	40	40
Sodium Citrate Dihydrate	pH Modifier	2.7	0.27
Sodium Chloride	Buffer Component	2.3	0.23

Inhalation Drug Product Dosing Unit Description

Capsule	Size 3 Opaque White HPMC Capsule			
Fill Description	White to Off-White Powder			
Fill Particle Shape	“pollen-shaped”			
Active Strength (µg)	0 (placebo)*	25	50	75
Formulation Powder per Capsule (mg)	15	5	10	15

*Excipients only (no treprostinil). Abbreviations: HPMC, hydroxypropyl methylcellulose

[0057] According to some embodiments of the present invention, drug particles are provided that include a composition having a target dose of 15 – 90 µg of delivered treprostinil to the patient (current TYVASO® label is 18-54 µg). In some embodiments of the present invention the dose of treprostinil provided to the patient can be, for example, 100 micrograms, 125 micrograms or 150 micrograms. In some embodiments of the present invention the dose of treprostinil provided to the patient, for example, can contain about 100 micrograms, about 125 micrograms or about 150 micrograms. In some embodiments, each dose contains greater than or equal to 200 micrograms of treprostinil. In some embodiments, each dose contains greater than or equal to 225 micrograms of treprostinil. In some embodiments, each dose contains greater than or equal to 250 micrograms of treprostinil. In some embodiments, each dose contains greater than or equal to 275 micrograms of treprostinil. In some embodiments, each dose contains greater than or equal to 300 micrograms of treprostinil. In some embodiments, each dose contains from about 10 micrograms to about 15 micrograms, 15 micrograms to about 20 micrograms, 20 micrograms to about 25 micrograms, 25 micrograms to about 30 micrograms, about 30 micrograms to about 35 micrograms, about 35 micrograms to about 40 micrograms, about 40 micrograms to about 45 micrograms, about 45 micrograms to about 50 micrograms, about 50 micrograms to about 55 micrograms, about 55 micrograms to about 60 micrograms, about 60 micrograms to about 65 micrograms, about 65 micrograms to about 70 micrograms, about 70 micrograms to about 75 micrograms, about 75 micrograms to about 80 micrograms, about 80 micrograms to about 85 micrograms, about 85 micrograms to about 90 micrograms, about 90 micrograms to about 95 micrograms, about 95 micrograms to about 100 micrograms, or

about 100 micrograms to about 105 micrograms of treprostinil. In some embodiments, each dose contains from about 100 micrograms to about 110 micrograms, 110 micrograms to about 120 micrograms, 120 micrograms to about 130 micrograms, 130 micrograms to about 140 micrograms, about 140 micrograms to about 150 micrograms, about 150 micrograms to about 160 micrograms, about 160 micrograms to about 170 micrograms, about 170 micrograms to about 180 micrograms, about 180 micrograms to about 190 micrograms, about 190 micrograms to about 200 micrograms, about 200 micrograms to about 210 micrograms, about 210 micrograms to about 220 micrograms, about 220 micrograms to about 230 micrograms, about 230 micrograms to about 240 micrograms, about 240 micrograms to about 250 micrograms, about 250 micrograms to about 260 micrograms, about 260 micrograms to about 270 micrograms, about 270 micrograms to about 280 micrograms, about 280 micrograms to about 290 micrograms, about 290 micrograms to about 300 micrograms, about 300 micrograms to about 310 micrograms, about 310 micrograms to about 320 micrograms, about 320 micrograms to about 330 micrograms, about 330 micrograms to about 340 micrograms, or about 340 micrograms to about 350 micrograms of treprostinil. In some embodiments, each dose contains from about 25 micrograms to about 400 micrograms of treprostinil. In some embodiments, each dose contains from about 25 micrograms to about 350 micrograms of treprostinil. In some embodiments, each dose contains from about 25 micrograms to about 300 micrograms of treprostinil. In some embodiments, each dose contains from about 50 micrograms to about 300 micrograms of treprostinil. In some embodiments, each dose contains from about 75 micrograms to about 300 micrograms of treprostinil. In some embodiments, each dose contains from about 100 micrograms to about 300 micrograms of treprostinil. In some embodiments, each dose contains from about 125 micrograms to about 300 micrograms of treprostinil. In some embodiments, each dose contains from about 150 micrograms to about 300 micrograms of treprostinil. In some embodiments, each dose contains from about 175 micrograms to about 300 micrograms of treprostinil. In some embodiments, each dose contains from about 200 micrograms to about 300 micrograms of treprostinil. In some embodiments, each dose contains from about 225 micrograms to about 300 micrograms of treprostinil. In some embodiments, each dose contains from about 250 micrograms to about 300 micrograms of treprostinil. In some embodiments, each dose contains from about 275 micrograms to about 300 micrograms of treprostinil. In some embodiments, each dose contains from about 50 micrograms to about 75

micrograms of treprostinil. In some embodiments, each dose contains from about 50 micrograms to about 100 micrograms of treprostinil. In some embodiments, each dose contains from about 50 micrograms to about 150 micrograms of treprostinil. In some embodiments, each dose contains from about 75 micrograms to about 100 micrograms of treprostinil. In some embodiments, each dose contains from about 75 micrograms to about 125 micrograms of treprostinil. In some embodiments, each dose contains from about 75 micrograms to about 150 micrograms of treprostinil. In some embodiments, each dose contains from about 75 micrograms to about 175 micrograms of treprostinil. In some embodiments, each dose contains from about 75 micrograms to about 200 micrograms of treprostinil. In some embodiments, each dose contains from about 75 micrograms to about 225 micrograms of treprostinil. In some embodiments, each dose contains from about 75 micrograms to about 250 micrograms of treprostinil. In some embodiments, each dose contains from about 75 micrograms to about 275 micrograms of treprostinil. In some embodiments, each dose contains from about 75 micrograms to about 300 micrograms of treprostinil. In some embodiments, each dose contains from about 75 micrograms to about 325 micrograms of treprostinil. In some embodiments, each dose contains from about 75 micrograms to about 350 micrograms of treprostinil. In some embodiments, each dose contains from about 100 micrograms to about 125 micrograms of treprostinil. In some embodiments, each dose contains from about 100 micrograms to about 150 micrograms of treprostinil. In some embodiments, each dose contains from about 100 micrograms to about 175 micrograms of treprostinil. In some embodiments, each dose contains from about 100 micrograms to about 200 micrograms of treprostinil. In some embodiments, each dose contains from about 100 micrograms to about 225 micrograms of treprostinil. In some embodiments, each dose contains from about 100 micrograms to about 250 micrograms of treprostinil. In some embodiments, each dose contains from about 100 micrograms to about 275 micrograms of treprostinil. In some embodiments, each dose contains from about 100 micrograms to about 300 micrograms of treprostinil. In some embodiments, each dose contains from about 100 micrograms to about 325 micrograms of treprostinil. In some embodiments, each dose contains from about 100 micrograms to about 350 micrograms of treprostinil. In some embodiments, each dose contains from about 125 micrograms to about 150 micrograms of treprostinil. In some embodiments, each dose contains from about 125 micrograms to about 175 micrograms of treprostinil. In some embodiments, each dose contains from about 125

micrograms to about 200 micrograms of treprostinil. In some embodiments, each dose contains from about 125 micrograms to about 225 micrograms of treprostinil. In some embodiments, each dose contains from about 125 micrograms to about 250 micrograms of treprostinil. In some embodiments, each dose contains from about 125 micrograms to about 275 micrograms of treprostinil. In some embodiments, each dose contains from about 125 micrograms to about 300 micrograms of treprostinil. In some embodiments, each dose contains from about 125 micrograms to about 325 micrograms of treprostinil. In some embodiments, each dose contains from about 125 micrograms to about 350 micrograms of treprostinil. In some embodiments, each dose contains from about 150 micrograms to about 175 micrograms of treprostinil. In some embodiments, each dose contains from about 150 micrograms to about 200 micrograms of treprostinil. In some embodiments, each dose contains from about 150 micrograms to about 225 micrograms of treprostinil. In some embodiments, each dose contains from about 150 micrograms to about 250 micrograms of treprostinil. In some embodiments, each dose contains from about 150 micrograms to about 275 micrograms of treprostinil. In some embodiments, each dose contains from about 150 micrograms to about 300 micrograms of treprostinil. In some embodiments, each dose contains from about 150 micrograms to about 325 micrograms of treprostinil. In some embodiments, each dose contains from about 150 micrograms to about 350 micrograms of treprostinil. In some embodiments, each dose contains from about 175 micrograms to about 200 micrograms of treprostinil. In some embodiments, each dose contains from about 175 micrograms to about 225 micrograms of treprostinil. In some embodiments, each dose contains from about 175 micrograms to about 250 micrograms of treprostinil. In some embodiments, each dose contains from about 175 micrograms to about 275 micrograms of treprostinil. In some embodiments, each dose contains from about 175 micrograms to about 300 micrograms of treprostinil. In some embodiments, each dose contains from about 175 micrograms to about 325 micrograms of treprostinil. In some embodiments, each dose contains from about 175 micrograms to about 350 micrograms of treprostinil. In some embodiments, each dose contains from about 200 micrograms to about 225 micrograms of treprostinil. In some embodiments, each dose contains from about 200 micrograms to about 250 micrograms of treprostinil. In some embodiments, each dose contains from about 200 micrograms to about 275 micrograms of treprostinil. In some embodiments, each dose contains from about 200 micrograms to about 300 micrograms of treprostinil. In some embodiments, each dose contains

from about 200 micrograms to about 325 micrograms of treprostinil. In some embodiments, each dose contains from about 200 micrograms to about 350 micrograms of treprostinil. In some embodiments, each dose contains from about 225 micrograms to about 250 micrograms of treprostinil. In some embodiments, each dose contains from about 225 micrograms to about 275 micrograms of treprostinil. In some embodiments, each dose contains from about 225 micrograms to about 300 micrograms of treprostinil. In some embodiments, each dose contains from about 225 micrograms to about 325 micrograms of treprostinil. In some embodiments, each dose contains from about 225 micrograms to about 350 micrograms of treprostinil. In some embodiments, each dose contains from about 250 micrograms to about 275 micrograms of treprostinil. In some embodiments, each dose contains from about 250 micrograms to about 300 micrograms of treprostinil. In some embodiments, each dose contains from about 250 micrograms to about 325 micrograms of treprostinil. In some embodiments, each dose contains from about 250 micrograms to about 350 micrograms of treprostinil. In some embodiments, each dose contains from about 275 micrograms to about 300 micrograms of treprostinil. In some embodiments, each dose contains from about 275 micrograms to about 325 micrograms of treprostinil. In some embodiments, each dose contains from about 275 micrograms to about 350 micrograms of treprostinil. In some embodiments, each dose contains from about 300 micrograms to about 325 micrograms of treprostinil. In some embodiments, each dose contains from about 300 micrograms to about 350 micrograms of treprostinil. In some embodiments, each dose contains from about 325 micrograms to about 350 micrograms of treprostinil. In some embodiments, each dose contains from about 350 micrograms to about 375 micrograms of treprostinil. In some embodiments, each dose contains from about 375 micrograms to about 400 micrograms of treprostinil. In some embodiments, a patient may be provided with one, two, three, four, or more doses per day. In some embodiments, a patient may be provided up to one, two, three, or four doses per day. Each dose may be contained in a single capsule according to some embodiments, for example, a HPMC capsule (size 3). In other embodiments, a dose may be made up of a combination of lower dose capsules. In some embodiments, a patient may be provided with four doses per day to match the current treatment cycle (nebulized treprostinil) however the drug dose per treatment cycle under the present invention dry powder provides significantly higher dose levels to be safely administered, such as for example, up to 100 mcg of treprostinil per dosing, up to 125 mcg of treprostinil and up to 150 mcg of treprostinil per dosing

as each were surprisingly demonstrated in the first clinical trial of LIQ861. In alternative embodiments, a patient may be provided with four doses per day to match the current treatment cycle (nebulized treprostinil) however the drug dose per treatment cycle under the present invention dry powder provides significantly higher dose levels to be achieved, such as for example, up to 200 mcg of treprostinil per dosing and up to 300 mcg of treprostinil per dosing as surprisingly demonstrated in pre-clinical toxicology studies using LIQ861.

[0058] Treprostinil itself is poorly soluble in unbuffered water and low pH buffers. However, the solubility improves with increasing pH as the carboxylic acid is deprotonated. The sodium salt was selected for use in this product since it enhances dissolution in aqueous media and facilitates processing.

[0059] Excipients

[0060] According to some embodiments of the present invention, the DP-intermediate (anhydrous) is comprised of particles that include, for example, the following excipients: trehalose, polysorbate 80, L-leucine, sodium citrate, and sodium chloride. In some embodiments, the ratio of treprostinil sodium and excipients is 0.581:92.32:2.19:4.39:0.26:0.25 (wt:wt solids) treprostinil sodium:trehalose:polysorbate 80:leucine:sodium citrate:sodium chloride. A summary of the function, quantity, and compendial status of these excipients is provided herein.

[0061] The excipients were selected based upon the following functional requirements for the formulation:

- **Trehalose Dihydrate:** Trehalose comprises the bulk of the particle and was selected because it is a non-reducing sugar with a high glass transition temperature. Trehalose is an example of a non-reducing sugar (as opposed to lactose, which is a reducing sugar) that can be used in the present invention. Trehalose is more chemically compatible with compounds containing primary amines, such as leucine.
- **Ultra-Pure Polysorbate 80 (Ultra-Pure Tween 80):** Polysorbate 80 is added as a processing aide / wetting agent to facilitate particle manufacturing. In some embodiments, Polysorbate 80 is a particle processing aide and enables film generation

during particle manufacture by decreasing dewetting, leading to uniform particle morphology.

- L-leucine: Leucine is added as a hydrophobicity and surface modifier to reduce the hygroscopicity of the particle and improve aerosol efficiency. L-leucine is an example of a formulation additive to reduce hygroscopicity to improve stability of the final drug product powder.
- Sodium chloride and sodium citrate: Sodium citrate and sodium chloride are used to buffer the stock solution used in the PRINT Technology manufacturing process and to help control acidity in the particle. Sodium chloride and sodium citrate are examples of buffers that help maintain pH and control ionization/acidity of the formulation. In some embodiments of the present invention, pH is maintained between about pH 6.0 and 7.2.

[0062] In addition to the active pharmaceutical ingredient the present drug particle comprises a bulking agent, wetting agent, hydrophobicity modifier, pH modifier and buffer. In some embodiments, the present drug particle comprises, along with the active ingredients, a bulking agent, hydrophobicity controlling agent, and a pH controlling agent.

[0063] According to another embodiment of the present invention, LIQ861 contains five excipients as follows: treprostinil sodium:trehalose dihydrate:leucine:polysorbate 80:sodium citrate dihydrate:sodium chloride at ratios of 0.53:92.97:4:2:0.27:0.23. At an example treprostinil dose level of 100 µg/day of the present invention drug particles, a patient would receive the following daily excipient doses:

- 18.6 mg of trehalose dihydrate. Assuming a patient weighs 60 kg and has a lung mass of 1000 g, this is equivalent to 310 µg/kg and 18.6 µg/g of lung.
- 0.4 mg of polysorbate 80. Assuming a patient weighs 60 kg and has a lung mass of 1000 g, this is equivalent to 6.7 µg/kg and 0.4 µg/g of lung.
- 0.8 mg of leucine. Assuming a patient weighs 60 kg and has a lung mass of 1000 g, this is equivalent to 13.3 µg/kg and 0.8 µg/g of lung.

- 0.05 mg of sodium citrate and 0.05 mg of sodium chloride. Assuming a patient weighs 60 kg and has a lung mass of 1000 g, this is equivalent to 0.83 µg/kg for each compound and 0.05 µg/g of lung for each compound.

[0064] Formulation Development

[0065] According to embodiments of the present invention, LIQ861 has been developed as a novel formulation of treprostinil for the treatment of PAH. Treprostinil is currently approved for use in the treatment of PAH by subcutaneous, IV, oral, and inhalation routes of administration. TYVASO is currently the only marketed inhaled formulation of treprostinil and is formulated as a liquid solution for administration using a nebulizer. The nebulized treprostinil is dosed, at maintenance dose, of 6 mcg drug per breath over 9 breaths for a dose of 54 mcg per dosing session. The nebulized treprostinil also has a maximum tolerated dose of 84 mcg over a dosing session with 14 breaths.

[0066] LIQ861 is suitable for inhaled administration using a dry powder inhalation device. The physicochemical properties and performance characteristics, manufacturing process and packaging, and stability characteristics of the DP have been studied, and a suitable formulation has been identified for progression into human studies.

[0067] Physiochemical and Biological Properties

[0068] The “pollen-shaped” LIQ861 particles according to certain embodiments have an aerodynamic size to enable efficient delivery to the pulmonary arterioles ($1 \leq \text{MMAD} \leq 5\mu\text{m}$) with a high FPF to limit oropharyngeal deposition. A scanning electron microscopy (SEM) image of the “pollen-shaped” feature is provided in Figure 9. The formulation of example particles shown in Figure 9 is: treprostinil:trehalose:leucine:polysorbate 80:sodium citrate:sodium chloride (Batch LKI-1R-983-27). Example aerosol data for the active particles are also provided in the table below.

[0069] During the development of the LIQ861 formulation, the applicants tested other possible particle shapes and sizes (e.g., 1.5 µm donut, 3.0 µm donut). Based upon these studies, the applicants observed that the “pollen-shaped” feature resulted in a greater FPF, reduced

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MMAD, acceptable ED, and dose uniformity characteristics when compared to other features both with and without treprostinil.

Representative Aerosol Data (NGI) for Active Particles

Sample	MMAD (μm)	GSD	ED (% nominal)	FPF (% ED)
Treprostinil Sodium: Trehalose:Leucine:Polysorbate 80:Sodium Citrate:Sodium Chloride ("pollen-shaped")	1.88	1.99	64	83

Abbreviations: NGI, Next Generation Impactor™, MSP Corp.; MMAD, mass median aerodynamic diameter; GSD, geometric standard deviation; ED, emitted dose; FPF, fine particle fraction; wt, weight. Batch LKI-1R-0983-21.

[0070] Manufacture

[0071] The manufacturing of LIQ861 particles according to some embodiments of the present invention is described below. A process flow diagram for the particles (also referred to as DP-intermediate) according to some embodiments is shown in Figure 10.

[0072] In particular embodiments, the particles of the present disclosure are fabricated using PRINT® Technology (Liquidia Technologies, Inc., Morrisville, NC) particle fabrication. In particular, the particles are made by molding the materials intended to make up the particles in mold cavities.

[0073] In some embodiments, the molds can be polymer-based molds and the mold cavities can be formed into any desired shape and dimension. Uniquely, as the particles are formed in the cavities of the mold, the particles are highly uniform with respect to shape, size, and composition. Due to the consistency among the physical and compositional makeup of the particles of the present compositions, the compositions of the present disclosure provide highly uniform release rates and dosing ranges. Methods and materials that may be used for fabricating the particles according to embodiments of the present disclosure are further described and disclosed in issued patents and co-pending patent applications, each of which are incorporated herein by reference in its entirety: U.S. Pat. Nos. 8,518,316; 8,444,907; 8,420,124; 8,268,446; 8,263,129; 8,158,728; 8,128,393; 7,976,759; U.S. Pat. Application Publications Nos. 2013-0249138, 2013-0241107, 2013-0228950, 2013-0202729, 2013-0011618, 2013-0256354, 2012-

0189728, 2010-0003291, 2009-0165320, 2008-0131692; and pending U.S. Application Nos. 13/852,683 filed March 28, 2013 and 13/950,447 filed July 25, 2013.

[0074] Particle Fabrication

[0075] An aqueous stock solution is prepared at the desired total solids concentration. All other excipients are combined with treprostinil and then filtered prior to particle fabrication.

[0076] The stock solution is applied in a thin layer to a continuous polyethylene terephthalate (PET) substrate backing layer. Forced air heat is used to drive off the water resulting in a dry film of treprostinil and excipients. The dried film is then brought into contact with a mold film, having cavities of the desired shape and size which the drug product particles will mimic, at an elevated temperature. The drug/excipient blend flows into the cavities of the mold, conforming to the shape defined by the cavity. The result is a uniform array of particles adhered to a PET backing layer. The particles are then allowed to cool to room temperature as the roll is wound up for later collection.

[0077] In one example of the present drug particles, the following stock solution is used:

Stock solution components used for manufacture of treprostinil particles, according to an embodiment:

Stock component	Target Solution Concentration (Active)	Target Solution Concentration (Placebo)	Target
Trehalose	12%	12.7%	Adjusted based on mass balance of other formulation components
Leucine	0.52%	0.54%	0.52-0.54% (4% solids)
Treprostinil Sodium	0.069%	0 %	0.069% (0.53% solids)
Polysorbate 80	0.26%	0.27%	0.26-0.28% (2% solids)

Sodium Citrate	0.035%	0.037%	Maintain pH stock solution for stability of treprostinil
NaCl	0.030%	0.031%	Maintain tonicity of stock solution
Diluent (water)	87.0%	86.4%	86-91% evaluated; to coat appropriate formulation mass for processing and solubility of excipient component(s)

[0078] Dry Collection and Drying

[0079] Next, the particles are dry collected, the process of removing the molded particles from the PET backing layer and thereby creating a bulk powder. The mold is first separated from the PET backing layer, exposing the particle array attached to the PET backing layer. The particle array is then passed across a blade, in some embodiments a plastic blade, to dislodge the particles from the backing layer. The particles can then be collected into a bulk powder for further processing.

[0080] Humidity is controlled to less than 15% RH during collection, in some embodiments due to the hygroscopicity of the powder. Temperature is maintained at ambient, typically between 15 and 25°C.

[0081] Drying and Bulk Packaging

[0082] The drug particles are dried at less than or equal to 150 mTorr of nitrogen or dry air for at least 2 days in a benchtop lyophilizer at room temperature, according to some embodiments.

[0083] In some embodiments, the particles of the present invention are dried to less than about 10 percent water content. In some embodiments, the particles of the present invention are dried to less than about 5 percent water content. In further embodiments, the particles of the present invention are dried to less than about 4 percent water content. In still further embodiments, the

particles of the present invention are dried to less than about 2 percent water content. In a preferred embodiment, the product is dried to less than about 1 percent water content by Karl Fisher titration.

[0084] Batch-to-Batch Uniformity of Drug Particles

[0085] In some embodiments, the particle uniformity from batch-to-batch provides the present invention with an unexpected and exceptional advantage over the prior art. In certain embodiments, the uniformity within any given batch is unexpected and exceptionally advantageous over the prior art. The present invention includes highly conserved batch uniformity as shown in the following data. See the table below and also Figure 2.

Uniformity: Sample aerosol data (NGI) for active particles (PAH-1R-0974-010)

Sample	MMAD	GSD	ED (%rec)	FPF (%ED)	F345 (fill)
PAH-1R-0974-010-A1 First	1.74	1.88	81%	88%	42%
PAH-1R-0974-010-B1 Middle	1.80	1.87	78%	87%	44%
PAH-1R-0974-010-C1 Last	1.72	1.87	90%	89%	40%

In the example shown, fine particle fraction remained within plus/minus 1 percent within a single batch run.

[0086] Capsule Filling and Packaging

[0087] In some embodiments, HPMC capsules are filled with the DP-intermediate in a humidity controlled ISO 8 environment using an XCELODOSE[®] (Capsugel) instrument. The filled HPMC capsules are packaged in a low humidity environment. Ten capsules are placed in a DESICAP[®] Vial and closed with a DESICAP[®] Cap. The closed vial is then placed into a foil bag with a desiccant canister prior to heat sealing the foil bag to form the packaged drug product.

[0088] Stability studies

[0089] According to the formulation of the present drug particle, it was desired to minimize uncontrolled exposure to ambient humidity. The drug particles according to embodiments of the present invention are shown to be stable for at least 9 months when stored under controlled humidity conditions at 25°C/60%RH. In some embodiments, the drug particles are shown to be stable for at least 6 months when stored under controlled humidity conditions at 40°C/75%RH. In some embodiments, the drug particles are shown to be stable for at least 9 months when stored under desiccated conditions at 25°C/60%RH. In some embodiments, the drug particles are shown to be stable for at least 6 months when stored under desiccated conditions at 40°C/75%RH. Studies were conducted to determine the stability of the drug particles at 25 °C/60% RH and 40 °C/75% RH.

[0090] Prototype Stability Study

[0091] The purpose of the Prototype Stability Study was to evaluate the stability of drug particles in capsules. Both the 25 and 75 µg strengths were evaluated when stored at 25 °C/60% RH and 40 °C/75% RH. For the study, drug particles were placed into size 3 HPMC opaque capsules (Capsugel Vcaps). Ten filled capsules were placed into HDPE vials (Desicap) which were sealed with a stopper. The stoppered vial was placed into a foil overwrap with desiccant sachets.

[0092] Data for the 25 µg dose drug particles stored at 25°C/60%RH is shown in the table below.

Test	Specifications		Time Points				
			Initial	1 Month	3 Months	6 Months	9 Months
Assay	0.450 – 0.550% w/w Treprostinil as free acid (%)		0.489	0.520	0.493	0.494	0.486
Aerodynamic Particle Size Distribution	Report Results	MMAD (µm)	1.92	2.11	2.2	2.1	2.1
		GSD (µm)	1.72	1.67	1.6	1.6	1.7
		FPF (%)	87	84	82.9	83.6	83.6

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Delivered Dose Uniformity	Report Results	Average (µg)	19.9	21.6	19.65	19.47	18.86
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[0093] Data for the 25 µg dose drug particles stored at 40°C/75%RH is shown in the table below.

Test	Specifications		Time Points			
			Initial	1 Month	3 Months	6 Months
Assay	0.450 – 0.550% w/w Treprostinil as free acid (%)		0.489	0.512	0.502	0.492
Aerodynamic Particle Size Distribution	Report Results	MMAD (µm)	1.92	2.09	2.1	2.1
		GSD (µm)	1.72	1.65	1.6	1.6
		FPF (%)	87	85	84.8	84.7
Delivered Dose Uniformity	Report Results	Average (µg)	19.9	21.2	18.86	19.28

[0094] Data for the 75 µg dose drug particles stored at 25°C/60%RH is shown in the table below.

Test	Specifications		Time Points				
			Initial	1 Month	3 Months	6 Months	9 Months
Assay	0.450 – 0.550% w/w Treprostinil as free acid (%)		0.489	0.500	0.496	0.494	0.487
Aerodynamic Particle Size Distribution	Report Results	MMAD (µm)	2.13	2.17	2.2	2.2	2.2
		GSD (µm)	1.60	1.61	1.6	1.6	1.6
			85	84	84.2	83.7	82.3

		FPF (%)					
Delivered Dose Uniformity	Report Results	Average (µg)	63.6	63.0	60.76	59.62	60.01

[0095] Data for the 75 µg dose drug particles stored at 40°C/75%RH is shown in the table below.

Test	Specifications		Time Points			
			Initial	1 Month	3 Months	6 Months
Assay	0.450 – 0.550% w/w Treprostinil as free acid (%)		0.489	0.509	0.506	0.491
Aerodynamic Particle Size Distribution	Report Results	MMAD (µm)	2.13	2.14	2.2	2.1
		GSD (µm)	1.60	1.61	1.6	1.6
		FPF (%)	85	85	84.8	85.3
Delivered Dose Uniformity	Report Results	Average (µg)	63.6	61.0	59.86	59.42

[0096] Clinical Trial Material Stability Study

[0097] The purpose of the Clinical Trial Material Stability Study was to evaluate the stability of drug particles in capsules. Three strengths were evaluated: 25, 50, and 75 µg active agent doses within capsules. As in the previous study, two storage conditions were evaluated: 25 °C/60% RH and 40 °C/75% RH. For the study, drug particles were placed into size 3 HPMC opaque capsules (Capsugel Vcaps). Ten filled capsules were placed into HDPE vials (DESICAP) which were sealed with a stopper. The stoppered vial was placed into a foil overwrap with desiccant sachets.

[0098] Data for the 25 µg dose drug particles stored at 25°C/60%RH is shown in the table below.

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Test	Specifications		Time Points			
			Initial	1 Month	3 Months	6 Months
Assay	0.450 – 0.550% w/w Treprostinil as free acid (%)		0.520	0.505	0.504	0.504
Aerodynamic Particle Size Distribution	Report Results	MMAD (µm)	2.3	2.3	2.2	2.1
		GSD (µm)	1.6	1.6	1.6	1.6
		FPF (%)	84.1	82.7	83.6	85.0
Delivered Dose Uniformity	Report Results (µg)	Average (µg)	19.784	20.48	19.24	19.47

[0099] Data for the 25 µg dose drug particles stored at 40°C/75%RH is shown in the table below.

Test	Specifications		Time Points			
			Initial	1 Month	3 Months	6 Months
Assay	0.450 – 0.550% w/w Treprostinil as free acid (%)		0.520	0.518	0.501	0.506
Aerodynamic Particle Size Distribution	Report Results	MMAD (µm)	2.3	2.2	2.2	2.2
		GSD (µm)	1.6	1.6	1.6	1.6
		FPF (%)	84.1	84.1	85.8	84.7
Delivered Dose Uniformity	Report Results	Average (µg)	19.784	20.73	18.89	18.80

[00100] Data for the 50 µg dose drug particles stored at 25°C/60%RH is shown in the table below.

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Test	Specifications		Time Points			
			Initial	1 Month	3 Months	6 Months
Assay	0.450 – 0.550% w/w Treprostinil as free acid (%)		0.515	0.509	0.509	0.506
Aerodynamic Particle Size Distribution	Report Results	MMAD (µm)	2.2	2.2	2.2	2.2
		GSD (µm)	1.6	1.6	1.6	1.6
		FPF (%)	86.2	85.6	85.7	85.3
Delivered Dose Uniformity	Report Results (µg)	Average (µg)	40.417	40.75	39.14	40.05

[00101] Data for the 50 µg dose drug particles stored at 40°C/75%RH is shown in the table below.

Test	Specifications		Time Points			
			Initial	1 Month	3 Months	6 Months
Assay	0.450 – 0.550% w/w Treprostinil as free acid (%)		0.515	0.520	0.505	0.501
Aerodynamic Particle Size Distribution	Report Results	MMAD (µm)	2.2	2.2	2.2	2.2
		GSD (µm)	1.6	1.6	1.6	1.6
		FPF (%)	86.2	86.5	86.2	84.1
Delivered Dose Uniformity	Report Results	Average (µg)	40.417	39.55	38.96	37.50

[00102] Data for the 75 µg dose drug particles stored at 25°C/60%RH is shown in the table below.

Test	Specifications		Time Points			
			Initial	1 Month	3 Months	6 Months
Assay	0.450 – 0.550% w/w Treprostinil as free acid (%)		0.517	0.512	0.509	0.508
Aerodynamic Particle Size Distribution	Report Results	MMAD (µm)	2.3	2.3	2.3	2.2
		GSD (µm)	1.6	1.6	1.6	1.6
		FPF (%)	84.8	84.1	84.5	85.1
Delivered Dose Uniformity	Report Results (µg)	Average (µg)	61.851	63.91	59.88	60.25

[00103] Data for the 75 µg dose drug particles stored at 40°C/75%RH is shown in the table below.

Test	Specifications		Time Points			
			Initial	1 Month	3 Months	6 Months
Assay	0.450 – 0.550% w/w Treprostinil as free acid (%)		0.517	0.513	0.503	0.495
Aerodynamic Particle Size Distribution	Report Results	MMAD (µm)	2.3	2.3	2.2	2.2
		GSD (µm)	1.6	1.6	1.6	1.6
		FPF (%)	84.8	85.1	85.8	84.9
Delivered Dose Uniformity	Report Results	Average (µg)	61.851	61.94	58.61	58.17

[00104] Dry Powder Inhalation Device

[00105] The RS00 Model 8 is a commercially available monodose dry powder inhalation device that is manufactured by Plastiaple S.p.A (Italy) in accordance with ISO and FDA standards. The overall design of RS00 Model 8 device is shown in Figure 11.

[00106] A cap, which is retained on the mouthpiece, is designed to prevent ingress of dirt and other foreign material into the inhaler when not in use. The plastic side portions cover the air inlet holes, but the cap does not provide a hermetic seal to the device. The cap does not form part of the actuation process.

[00107] When assembled, the mouthpiece is mounted on the inhaler body, but is removable for cleaning purposes. To assemble the mouthpiece, the off-set peg at the base of the mouthpiece is placed into the corresponding hole in the inhaler body and the mouthpiece is rotated until it snaps closed. The snap closure ensures that the mouthpiece and inhaler body are properly aligned and that no spurious airflow occurs. The mouthpiece contains a mesh that aids particle size reduction and prevent capsule ingestion during inhalation.

[00108] The inhaler body component contains two side buttons, each housing four pins for piercing a capsule. The pins are inserted in the corresponding housing of the pushbuttons and the heads of the pins are retained in their position by a back-plate that is ultrasonically welded to the pushbutton. The buttons and pins are each maintained in their outward position by four small steel springs in each button. A three-component snap-lock system on the inhaler body ensures correct alignment of the mouthpiece when closed.

[00109] A capsule piercing area is located internally, adjacent to the pins. When a capsule is inserted in this area, depressing the buttons causes the button pins to pierce the capsule ends, thereby preparing the capsule for emptying. Above the capsule piercing area, there are 2 tangential air inlets and a circular chamber. These allow the capsule to spin when the patient inhales through the device. Capsule spinning creates a centrifugal effect on the powder that promotes efficient emptying.

[00110] The performance of the premetered dry powder inhaler is a combination of the characteristics of LIQ861 (including the powder and capsule) and the inhalation device itself.

[00111] NONCLINICAL STUDIES

[00112] Treprostinil is a tricyclic benzidine analogue of endogenous PGI₂. The major pharmacologic actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation. It was developed for chronic administration as a continuous subcutaneous infusion as a treatment for patients with PAH. PGI₂, an endothelial cell derived substance, is a potent vasodilator and inhibitor of platelet aggregation. The hemodynamic properties of treprostinil are similar to those of PGI₂ but, unlike PGI₂, treprostinil is chemically stable.

[00113] A series of *in vivo* studies were conducted to evaluate pharmacokinetics (PK) and toxicology of the present invention dry powder treprostinil formulation.

[00114] Pilot, non-GLP, single-dose, inhalation PK study of treprostinil in dogs (Study 19073)

[00115] This study compared the single dose PK of LIQ861 (administered via DPI) to Tyvaso (administered via nebulizer) at a target lung deposition of 3 µg/kg in 3 beagle dogs. Results showed generally similar treprostinil PK profiles following dosing with LIQ861 compared with Tyvaso. In this pilot single administration PK study, treprostinil (dry powder formulation; estimated lung deposition of 3.0 to 3.4 µg/kg) and treprostinil (nebulized liquid; target lung deposition of 3 µg/kg) were compared in 3 beagle dogs. The results showed generally similar treprostinil PK profiles following dosing with treprostinil (dry powder formulation) compared with treprostinil (nebulized liquid). The study design and results are discussed in more detail herein.

[00116] The applicants conducted a study comparing plasma concentrations and pharmacodynamics (PD) following administration of treprostinil sodium (nebulized liquid versus a dry powder formulation similar to the LIQ861 formulation of the present invention) as a single inhalation exposure (via controlled ventilation) to anesthetized beagle dogs. Treprostinil sodium was prepared as a nebulized liquid from the same DS used to prepare the dry powder formulation. The dry powder formulation was manufactured using PRINT Technology and utilized the same drug substance, treprostinil sodium, but was different in excipient concentrations compared to LIQ861. Importantly, the excipient concentrations of the present invention provide highly consistent and reproducible batch to batch manufacturing of the

LIQ861 product. The formulations used in this study will be referred to as treprostinil (nebulized liquid) and treprostinil (dry powder formulation), respectively, in description of this study. The study design, results, and conclusions are described below.

[00117] In study 19073, 3 dogs received a single inhalation administration of nebulized treprostinil (nebulized liquid; estimated lung deposition of 3.4 µg/kg). After a 2-day washout, the dogs received a single inhalation administration of treprostinil (dry powder formulation; estimated lung deposition of 3.0 to 3.4 µg/kg). Blood was collected for plasma analysis of treprostinil concentrations prior to each administration and at 2, 5, 10, 20, 30, 60, 120, and 180 minutes after the completion of each administration. In addition, 2 different dogs (one assigned to each treprostinil formulation) were used to monitor the following PD endpoints (hemodynamic changes): systemic arterial blood pressures [mean arterial pressure (MAP, mmHg), systolic arterial pressure (mmHg), diastolic arterial pressure (mmHg)], pulmonary artery pressure (PAP, mmHg), right atrial pressure (RAP, mmHg), pulmonary capillary wedge pressure (PCWP, mmHg) or left atrial pressure (mmHg), cardiac output (CO, L/min the average of 3), total peripheral resistance (TPR), pulmonary vascular resistance (PVR), and heart rate (HR). The PD effects were assessed prior to initiation of dose administration and at target times of 5, 10, 20, 30, 60, 120, and 180 minutes after the completion of the administration. In contrast to the first three dogs, the dogs assigned to monitor the PD effects were anesthetized for the duration of data collection. The dog assigned treprostinil (nebulized liquid) received an estimated lung deposition of 4.0 µg/kg and the dog assigned to treprostinil (dry powder formulation) received an estimated lung deposition of 2.5 µg/kg. Blood was collected at the same time points as first 3 dogs.

[00118] Treprostinil (nebulized liquid and dry powder formulation) had no effect on HR, PAP, RAP, PCWP, or CO, but had a slight effect on decreasing and then increasing arterial blood pressure. Treprostinil (nebulized liquid) appeared to decrease stroke volume, increase TPR, and decrease PVR. Treprostinil (dry powder formulation) appeared to increase stroke volume, decrease TPR, and decrease PVR. The Study Director concluded that the pilot data were inconclusive for comparing the potential PD effects of treprostinil (nebulized liquid) to the treprostinil (dry powder formulation) formulation; however, there appeared to be no important differences in PD effects associated with administration of treprostinil in either formulation.

[00119] Pilot, non-GLP, single-dose, inhalation PK study of LIQ861 in male rats (Study 75670)

[00120] This study evaluated the PK of treprostinil in male rats following single inhalation of a range of LIQ861 doses up to a feasible dose. Systemic exposure data from this study was used to determine appropriate doses and blood sampling times for a definitive, comparative PK bridging study of LIQ861 and nebulized treprostinil. Results from this study were used to select dose levels and an optimal blood sampling paradigm for a definitive PK bridging study.

[00121] SUMMARY: STUDY 75670

[00122] The objective of the study was to determine the pharmacokinetic profile of treprostinil in male Sprague Dawley rats when administered as the test item, PRINT Treprostinil dry powder (PRINT-Tre), as a single 4 hour inhalation at targeted dose levels of 0.15, 0.75, and 1.5 mg/kg. Results from this study will be used to determine appropriate dose levels and sampling time points for a definitive PK bridging study.

[00123] The test item was administered once by inhalation to 3 male rats per group as described in the table below:

Group No.	Group Designation	Achieved Mean Total Inhaled Dose Level of Treprostinil (mg/kg/day)	Achieved Aerosol Concentration of Treprostinil (µg/L)	Achieved Aerosol Concentration of Trehalose (µg/L)
1	Low Dose	0.158	1.06	150.46
2	Mid Dose	0.707	4.72	664.85
3	High Dose	1.409	9.39	1298.81

[00124] Assessments of mortality, clinical signs and body weights were performed. Blood samples were collected and analyzed for treprostinil content.

[00125] No mortality occurred. No clinical signs were observed and body weights were unaffected.

[00126] The overall achieved gravimetric and analytical aerosol concentrations for all groups were within 16% of the targeted concentrations. Corresponding average treprostinil dose levels for all groups were within 7% of the targeted dose levels and a clear dose differentiation between groups for each sex was achieved. The gravimetric particle size MMADs from all groups were between 1.2 and 1.6 μm (GSD 2.06 to 2.56). For both treprostinil and trehalose, the chemical determination of particle size distribution ranged from 1.3 to 1.8 μm with the corresponding GSDs between 1.65 and 2.15. The particle size distribution was considered respirable gravimetrically and chemically.

[00127] Mean PK parameters for PRINT-Tre treatment groups obtained by non-compartmental analysis of the mean treprostinil plasma concentration data sets are summarized as follows:

Group		$T_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ng/mL)	$\text{AUC}_{0-\text{Tlast}}$ (hr*ng/mL)	AUC_{INF} (hr*ng/mL)
1	Mean	1.01	3.75	6.800	17.320	18.335
	SD	0.521	0.00	0.951	2.281	1.806
	N	3	3	3	3	3
2	Mean	1.68	3.75	31.933	81.289	93.369
	SD	0.967	0.00	9.500	19.478	19.372
	N	3	3	3	3	3
3	Mean	1.48	3.75	46.130	121.285	137.512
	SD	0.619	0.00	20.580	53.331	53.418
	N	3	3	3	3	3

[00128] In conclusion, single inhalation administration for 4 hours of PRINT-Tre at a high average treprostinil dose of 1.409 mg/kg/day by Sprague-Dawley rats was well tolerated as there were no significant test item related findings. The exposure to treprostinil generally increased in a dose proportional manner between the low dose and the mid dose. The exposure between the mid and high dose increased in a slightly less than dose proportional manner. However, animals in the high dose group were exposed to aerosol concentrations far below target for the last 16 to 26 minutes of inhalation, which may account for the less than dose proportional increase in

exposure. Based on these results, similar dose levels are recommended for the following definitive PK study. Blood sampling time points during the test item inhalation period may be adjusted so as to better characterize exposure during test item administration.

[00129] INTRODUCTION

[00130] The objective of the study was to determine the pharmacokinetic profile of treprostinil in male Sprague Dawley rats when administered as the test item, PRINT Treprostinil dry powder (PRINT-Tre), as a single 4 hour inhalation at targeted dose levels of 0.15, 0.75, and 1.5 mg/kg. Results from this study will be used to determine appropriate dose levels and sampling time points for a definitive PK bridging study.

[00131] The study was not performed in compliance with GLP regulations but followed appropriate Standard Operating Procedures (SOPs).

[00132] EXPERIMENTAL DESIGN

[00133] The test item was administered to groups of rats by inhalation administration for one day as described in the table below:

Group No.	Group Designation	Targeted Total Inhaled Dose Level of Treprostinil (mg/kg/day) ^a	Targeted Aerosol Concentration of Treprostinil (µg/L)	Targeted Aerosol Concentration of Trehalose (µg/L)	No. of Animals
					Males
1	Low Dose	0.15	1	130.7	3
2	Mid Dose	0.75	5	653.5	3
3	High Dose	1.5	10	1306.9	3

^a = Targeted aerosol concentrations were calculated based on an estimated body weight of 0.250 kg

[00134] Following dosing, a series of 6 blood samples for pharmacokinetic evaluation were taken.

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- Characterization of Test Item

Test item*:	Identity:	PRINT Treprostinil
	Content:	92.75% of Trehalose, 4% of Leucine, 2% of Tween80, 0.26% of NA Citrate Dihydrate, 0.25% of NaCl : 0.74% of Treprostinil sodium (0.67% treprostinil)
	Storage Conditions:	Cool (2 to 8°C), protect from moisture (e.g., dessicant)
	Handling Precautions:	Standard laboratory precautions. Handle under dry conditions (Relative Humidity \leq 23%)
	Supplier:	Liquidia Technologies Inc.

[00135] TREATMENT

[00136] Acclimatization to Exposure System

[00137] Before the animals were exposed to the aerosol of the test item, rats were accustomed to the restraint procedure over a period of 3 days. The animals were gradually accustomed to restraint in the dosing tubes used during the exposures up to the duration that was used for aerosol administrations.

[00138] Animal Exposure

Exposure system used:	Flow-past rodent inhalation exposure system
Exposure method:	Inhalation by nose-only exposure
Test Item type:	Dry-Powder formulation
Generation method:	Piston feed/rotating brush generator
Duration of exposure:	240 minutes

[00139] The target aerosol concentrations and dose levels were as follows:

Group No.	Group Designation	Targeted Dose Level of Treprostinil (mg/kg/day) ^a	Targeted Aerosol Concentration of Treprostinil (µg/L)	Targeted Aerosol Concentration of Trehalose (µg/L)
1	Low Dose	0.15	1	130.7
2	Mid Dose	0.75	5	653.5
3	High Dose	1.5	10	1306.9

a = Target aerosol concentrations were calculated based on an estimated body weight of 0.250 kg.

[00140] ESTIMATION OF ACHIEVED DOSE LEVELS

The target dose levels were estimated using the following formula:

$$D_L = \frac{E_c \times RMV \times T}{BW}$$

D_L = Achieved dose levels (mg / kg / day)

E_c = Actual concentration delivered to the animals (mg / L air)

RMV = Respiratory Minute Volume (L / min) according to the method of Bide, Armour and Yee J. App. Toxicol., Vol. 20, 2000: RMV (L / min) = $0.499 \times BW$ (kg)^{0.809}

T = Time, duration of daily exposure (min.)

BW = Mean body weight (kg) during exposure period.

This estimation of total inhaled dose assumed 100% deposition within the respiratory tract.

[00141] Inhalation Exposure System

[00142] The powder aerosol was produced using a piston feed / rotating brush generator. The aerosol produced was diluted as necessary to achieve the target aerosol concentration and discharged through a 40-mm diameter tube into a flow-past inhalation exposure system. The airflow rate through the exposure system was monitored and recorded manually during each aerosol generation period. Airflow to the exposure system was controlled by the absolute volume of air supplying the generation apparatus using variable area flowmeters. Control of the

aerosol exhaust flow from the animal exposure system was achieved using an exhaust valve, and the overall balance of airflows in the exposure system was monitored using pressure gauges. The system provided a minimum of 1.0 L/min to each animal exposure port and was balanced to ensure a slight positive pressure at the site of the proposed animal exposure. This ensured that there was no dilution of the generated aerosol. An equal delivery of aerosol to each proposed exposure position was achieved by employing a distribution network that was identical for each individual exposure position attached to the system.

[00143] Inhalation System Monitoring

[00144] Determinations of aerosol concentration, particle size distribution, oxygen concentration, relative humidity and temperature were measured on samples collected from a representative port of the exposure chamber. The sample flow rates were precisely controlled using variable area flow meters that were calibrated before use using a primary airflow calibrator. The absolute volume of each aerosol concentration sample was measured with a wet type gas meter.

[00145] Oxygen Concentration

[00146] The oxygen concentration of the generated atmosphere was measured once during each aerosol exposure. Oxygen concentrations of the exposure atmospheres were maintained between 19-23%.

[00147] Relative Humidity/Temperature

[00148] The temperature and relative humidity of the generated atmosphere were measured once during each aerosol exposure. Temperatures of the exposure atmospheres were maintained between 19-24°C.

[00149] Determination of Aerosol Concentration

[00150] At least one aerosol concentration filter sample was collected on glass fiber filter and weighed on each day in order to measure the gravimetric concentration of the test item in the generated aerosol. The filter samples were transferred to the analytical chemistry laboratory for

chemical determination of Treprostinil and Trehalose concentrations using an analytical method (Study No. 41609 and Study No. 41635).

[00151] Determination of the Particle Size Distribution and Mass Median Aerodynamic Diameter (MMAD)

[00152] The distribution of particle size in the generated aerosols was measured once during each exposure by collecting samples into a 7-Stage Mercer Cascade Impactor. The MMAD and the Geometric Standard Deviation (GSD) were calculated based on the results obtained from the impactor using a log-probit transformation.

[00153] IN-LIFE OBSERVATIONS

[00154] Mortality

[00155] Mortality checks were performed at least once a day during all phases of the study.

[00156] Clinical Observations

[00157] Cage-side clinical signs (ill health, behavioral changes etc.) were recorded at least once daily during all phases of the study, except on detailed clinical examination days, where the cage-side clinical signs were replaced by a DCE.

[00158] A detailed clinical examination of each rat was performed on arrival as part of the health status, as well as on Day 1, prior to dosing.

[00159] Animal whose health status was judged to warrant additional evaluation was examined by a Clinical Veterinarian.

[00160] Body Weights

[00161] Body weights were recorded for all animals once at arrival as per health status, once prior to group assignment and on Day 1 (prior to dosing).

[00162] Pharmacokinetics

[00163] A series of 6 blood samples (approximately 0.3 mL each) was collected from each rat on Day 1 at -15, 5, 15, 30, 75 and 105 minutes after treatment. Thus a total blood volume of 1.8 mL was taken from each rat during the course of the study. For this purpose, each rat (unanesthetized) was bled by jugular venipuncture and the samples were collected into tubes containing the anticoagulant, K₂EDTA. Tubes were placed on wet ice pending processing.

[00164] Following collection, the samples were centrifuged (2500 rpm for 10 minutes at approximately 4°C) and the resulting plasma was recovered and stored frozen ($\leq -60^{\circ}\text{C}$) in labeled tubes.

[00165] Deviations to the pharmacokinetic time points were noted in the raw data and were made available with the samples. The location of blood withdrawal was noted in the raw data.

[00166] Non-compartmental analysis of treprostinil concentrations in plasma were performed by using the Phoenix WinNonlin 6.3 software.

[00167] The following configuration was used for the analysis:

Sampling Method:	Sparse
AUC Calculation Method:	Linear Trapezoidal with Linear Interpolation
Lambda Z (λ_z) Method:	Best fit for λ_z , Log regression
Weighting (λ_z calculation):	Uniform

[00168] Pharmacokinetic parameters (including abbreviation and description for each parameter) are described in the following table:

Parameters	Abbreviation	Unit*
Area under the plasma drug concentration-time curve from the time of dosing to the last quantifiable concentration	AUC _{0-Tlast}	µg*hr/mL
Area under the plasma drug concentration-time curve from the time of dosing extrapolated to infinity	AUC _{INF}	µg*hr/mL
Terminal elimination half-life	T _{1/2}	hr
The maximum plasma concentration	C _{max}	µg/mL
Time to maximum plasma concentration	T _{max}	hr

*Different units may be presented in the study report

[00169] DATA EVALUATION AND STATISTICS

[00170] Numeric and non-numeric data obtained during the study were reported only as individual values.

[00171] RESULTS

[00172] Aerosol Concentrations

[00173] Achieved gravimetric test atmosphere concentrations were as follows:

Group No.	Targeted Aerosol Concentration (mg/L)	Achieved Mean Aerosol Concentration (mg/L)	Coefficient of Variation (%)	% of Target
1	0.156	0.165	17.2	105.9
2	0.781	0.728	14.0	93.2
3	1.563	1.439	43.5	92.0

[00174] Achieved analytical test atmosphere concentrations for treprostinil were as follows:

Group No.	Targeted Aerosol Concentration (µg/L)	Achieved Mean Aerosol Concentration (µg/L)	Coefficient of Variation (%)	% of Target
1	1	1.06	17.6	105.9

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2	5	4.72	13.9	94.4
3	10	9.39	43.6	93.9

[00175] Achieved analytical test atmosphere concentrations for trehalose were as follows:

Group No.	Targeted Aerosol Concentration (µg/L)	Achieved Mean Aerosol Concentration (µg/L)	Coefficient of Variation (%)	% of Target
1	130.7	150.46	18.8	115.1
2	653.5	664.85	15.0	101.7
3	1306.9	1298.81*	44.1	99.4

*Last 2 aerosol concentrations samples for trehalose were estimated with a 92.79% difference from gravimetric data as analytical results were BLQ

[00176] The overall achieved gravimetric and analytical aerosol concentrations for all groups were within 16% of the targeted concentrations. The generated atmospheres were considered stable over the treatment period as % CV were all below 20%, except for Group 3. The increased % CV for Group 3 was caused by the stoppage of the Rotating Brush Generator (RBG) due to lack of test item remaining in the canister with 26 minutes left in the generation (16 minutes of dosing left for animal 3001A, 21 minutes left for animal 3002A and 26 minutes left for animal 3003A). Though a new test item canister was installed on the RBG apparatus, the aerosol concentrations were much lower than targeted for the last 26 minutes. However, the overall aerosol concentrations were still considered acceptable for the study as there was a significant difference in aerosol concentration between groups.

[00177] Dose Levels

[00178] Overall achieved doses for treprostinil are presented below:

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Group No.	Targeted Dose Levels (mg/kg/day)	Duration of Exposure (min)	Animal	Body Weight (kg)	Estimated Achieved Doses (mg/kg/day)	% from Targeted Dose Level
1	0.15	240	1001A	0.326	0.157	104.7
			1002A	0.309	0.159	106.0
			1003A	0.314	0.158	105.3
			<i>Average</i>		<i>0.158</i>	<i>105.3</i>
2	0.75	240	2001A	0.319	0.703	93.7
			2002A	0.308	0.708	94.4
			2003A	0.304	0.709	94.5
			<i>Average</i>		<i>0.707</i>	<i>94.3</i>
3	1.5	240	3001A	0.322	1.396	93.1
			3002A	0.321	1.397	93.1
			3003A	0.281	1.433	95.5
			<i>Average</i>		<i>1.409</i>	<i>93.9</i>

[00179] Average achieved dose levels for all groups were within 7% of the targeted dose levels therefore the dose levels were considered acceptable for the study as a clear dose differentiation between groups for each sex was achieved.

[00180] Particle Size Distribution

[00181] The average gravimetric particle size distribution measurement data were as follows:

Group No.	Cumulative % Less Than Stated Effective Cut-Off Diameter (µm)								Mean		% below 4 µm
	4.60	3.00	2.10	1.60	1.10	0.70	0.33	0.00	MMAD (µm)	GSD	
1	95.8	92.4	82.4	45.4	32.4	21.5	12.3	0.0	1.2	2.28	93
2	86.8	83.3	76.0	39.4	28.0	15.4	8.9	0.0	1.5	2.56	85

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3	94.0	90.9	77.3	30.3	13.4	8.9	5.3	0.0	1.6	2.06	90
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MMAD=Mass median aerodynamic diameter

GSD=Geometric standard deviation.

[00182] The average chemical determination of particle size distribution for treprostinil were as follows:

Group No.	Cumulative % Less Than Stated Effective Cut-Off Diameter (µm)								Mean		% below 4 µm
	4.60	3.00	2.10	1.60	1.10	0.70	0.33	0.00	MMAD (µm)	GSD	
1	96.4	93.9	83.3	42.8	28.1	16.5	6.9	0.0	1.3	2.06	94
2	91.7	88.5	81.1	37.9	25.8	11.8	4.9	0.0	1.5	2.15	90
3	95.2	91.5	76.6	25.7	8.8	5.1	1.8	0.0	1.7	1.86	91

MMAD=Mass median aerodynamic diameter

GSD=Geometric standard deviation.

[00183] The average chemical determination of particle size distribution for trehalose were as follows:

Group No.	Cumulative % Less Than Stated Effective Cut-Off Diameter (µm)								Mean		% below 4 µm
	4.60	3.00	2.10	1.60	1.10	0.70	0.33	0.00	MMAD (µm)	GSD	
1	95.8	91.6	81.5	38.4	24.1	13.0	4.2	0.0	1.4	2.01	93
2	94.4	88.9	83.3	31.5	26.0	11.1	5.6	0.0	1.4	2.11	91
3	95.2	90.4	77.0	25.5	9.6	4.8	0.0	0.0	1.8	1.65	94

MMAD=Mass median aerodynamic diameter

GSD=Geometric standard deviation.

[00184] The particle size distribution was considered respirable for this study as the MMADs were below 4 µm and the GSD were within 1.5 and 3.

[00185] Exposure Chamber Conditions

[00186] Exposure chamber conditions from the reported aerosol concentration exposures are summarized below.

Group No.	Humidity (%RH)	Temperature (°C)	Oxygen Concentration (%)
1	31.4	21.2	20.9
2	34.2	21.7	20.9
3	26.2	20.7	20.9

[00187] Exposure atmosphere oxygen concentrations, temperature and relative humidity ranges were considered acceptable on all occasions.

[00188] Mortality

[00189] There were no mortalities during the study.

[00190] Clinical Signs

[00191] There were no adverse clinical signs observed during the study.

[00192] Slight decreased activity, piloerection and partially closed eyes were seen in animal 3001A right before the 15 minute time point. However these were not observed afterwards and were not observed in any other animal therefore were not deemed test item related.

[00193] Body Weight

[00194] Body weights were performed for dose level calculation purposes.

[00195] Pharmacokinetics

[00196] Following the administration of PRINT-Tre at all achieved dose levels, mean C_{\max} ranged from 6.800 to 46.133 ng/mL. The mean maximum plasma concentration (T_{\max}) was reached at 3.75 hour (15 minutes before end of dosing) for all groups. The mean $AUC_{0-T_{\text{last}}}$ (AUC_{INF}) ranged from 17.320 (18.335) to 121.258 (137.512) hr*ng/mL. Following T_{\max} , the treprostinil plasma concentrations declined gradually with an estimated mean $T_{1/2}$ ranging from 1.01 to 1.68 hours.

[00197] Over the dose range, exposure to treprostinil (based on C_{\max} , $AUC_{0-T_{\text{last}}}$ and AUC_{INF}) generally increased in dose proportional manner between the low dose (0.158 mg/kg) and the mid dose (0.707 mg/kg). When dose level increased 4.5-fold from low to mid dose, C_{\max} and $AUC_{0-T_{\text{last}}}$ increased 4.7-fold. Treprostinil exposure between the mid dose (0.707 mg/kg) and high dose (1.409 mg/kg) increased in a slightly less than dose proportional manner (2-fold increase in dose with a 1.4- (C_{\max}) to 1.5-fold ($AUC_{0-T_{\text{last}}}$) increase in exposure). However, because animals in the high dose group were exposed to aerosol concentrations far below target for the last 16 to 26 minutes of the exposure period, exposure levels may have been effected and could account for the less than dose proportional increase in exposure.

[00198] CONCLUSION

[00199] Single inhalation administration for 4 hours of PRINT-Tre at a high average treprostinil dose of 1.409 mg/kg/day to Sprague-Dawley rats was well tolerated as there were no significant test item related findings. The exposure to treprostinil generally increased in a dose proportional manner between the low dose and the mid dose. The exposure between the mid and high dose increased in a slightly less than dose proportional manner. However, animals in the high dose group were exposed to aerosol concentrations far below target for the last 16 to 26 minutes of inhalation, which may account for the less than dose proportional increase in exposure. Based on these results, similar dose levels are recommended for the following definitive PK study. Blood sampling time points during the test item inhalation period may be adjusted so as to better characterize exposure during test item administration.

[00200] Non-GLP, single-dose, inhalation, comparative PK study of LIQ861 and nebulized treprostinil in rats (Study 75658)

[00201] This study evaluated and compared the PK profile of LIQ861 to treprostinil (nebulized) to establish a bridge between the two formulations.

[00202] The non-GLP, single administration by inhalation, PK study of treprostinil in rats (Study 75658) has been completed by Liquidia (referred to as the definitive PK bridging study). This study compared the systemic exposure of LIQ861 versus nebulized liquid treprostinil sodium. The observed systemic exposures revealed no meaningful differences between formulations, providing a bridge between the LIQ861 formulation and the marketed Tyvaso formulation and thereby permitting use of Tyvaso nonclinical toxicology studies to support the LIQ861 formulation per the 505(b)(2) pathway.

[00203] In Study 75658, systemic exposure of LIQ861 versus nebulized treprostinil sodium was compared in rats. LIQ861 was delivered over a 4-hour exposure period at total delivered dose levels of 0.273, 0.762, and 1.50 mg/kg body weight. Nebulized treprostinil sodium was delivered at a single dose level (0.785 mg/kg total delivered dose) for the same exposure period (4 hours) as LIQ861. Blood was collected for plasma analysis of treprostinil concentrations at 30 and 60 minutes following the start of administration, immediately post-administration (240 min), and at 5, 15, 30, 75, and 105 minutes following the end of administration.

[00204] Pharmacokinetic parameters from Study 75658. Individual plasma concentrations of treprostinil ranged from 0.345 to 67.4 ng/mL. Maximum plasma concentration was reached 0.5 to 4 hours after the start of the 4-hour exposure period. Maximum concentration (C_{max}) and area under the curve (AUC) values were similar between males and females within treatment groups. Dose-related increases in C_{max} and AUC values were observed for the three LIQ861 dose groups. Relative bioavailability of LIQ861 compared to nebulized treprostinil based on dose normalized AUC-time curve extrapolated to time infinity (AUC_{inf}) ranged from 1.2 to 2.2.

**Summary of Mean Noncompartmental PK Parameters by Treatment and Sex for Study
75658**

Type of inhalation	Group	Achieved Mean Dose Level (mg/kg)	Sex	R ²	t _{1/2} (hr)	T _{max} (hr)	C _{max} (ng/mL)	AUC _{0-Tlast} (hr*ng/mL)	AUC _{INF} (hr*ng/mL)
Treprostinil Sodium (Nebulized)	1	0.785	Female	0.99	0.59	4.00	16.2	62.4	63.5
			Male	0.97	0.77	0.50	16.5	59.3	60.6
Dry Powder (PRINT treprostinil)	2	0.273	Female	0.92	1.77	4.00	5.38	22.2	24.2
			Male	1.00	0.73	1.00	7.18	26.9	27.4
	3	0.762	Female	0.97	0.66	4.00	32.8	107	110
			Male	0.90	0.95	4.00	54.4	144	149
	4	1.498	Female	0.84	0.67	0.50	44.5	174	182
			Male	1.00	0.90	4.00	44.1	143	148

Abbreviations: C_{max}, maximal concentration; T_{max}, time of maximal concentration; AUC_{last}, area under the concentration-time curve to the last measured timepoint; t_{1/2}, half-life; AUC_{inf}, area under the concentration-time curve extrapolated to time infinity. PRINT treprostinil = LIQ861 DP-intermediate.

Calculated Relative Bioavailability (Combined Genders) Based on AUC_{inf} (Dose Corrected) from Study 75658

Group	Treatment	Dose Level (mg/kg)	Mean AUC _{inf} (hr*ng/mL)	F _{rel} (PRINT/Treprostinil)
1	Treprostinil	0.785	62.1	NA
2	PRINT-treprostinil Low	0.273	25.8	1.20
3	PRINT-treprostinil Mid	0.762	129	2.15

4	PRINT-treprostini High	1.498	165	1.39
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Abbreviations: AUCinf, area under the concentration-time curve extrapolated to time infinity; Frel, relative bioavailability; NA, not applicable. PRINT treprostini = LIQ861 DP-intermediate.

[00205] Summary: Study 75658

[00206] The objectives of the study were to determine the pharmacokinetic (PK) profile of Treprostini in Sprague-Dawley rats when administered as PRINT-Treprostini (PRINT-Tre) by 4-hour inhalation at 0.15, 0.75, and 1.5 mg/kg, to determine the PK profile of Treprostini in Sprague-Dawley rats when administered as nebulized Treprostini sodium in solution (Tre solution) by 4-hour inhalation at 0.75 mg/kg and to compare the PK profiles of Treprostini when administered as PRINT-Tre and Tre solution.

[00207] The test item was administered once to 6 male and 6 female rats per group by nose-only inhalation for 4 hours as described in the table below:

Group No.	Group Designation	Achieved Mean Total Inhaled Dose Level of Treprostini (mg/kg/day)	Achieved Aerosol Concentration of Treprostini (µg/L)	Achieved Aerosol Concentration of Trehalose (µg/L)
1	Tre Solution	0.785	5.07	0
2	PRINT-Tre (Low Dose)	0.273	1.76	254.84
3	PRINT-Tre (Mid Dose)	0.762	4.95	719.53
4	PRINT-Tre (High Dose)	1.498	9.73	1394.33

[00208] Assessments of mortality, clinical signs and body weights were performed. Pharmacokinetic samples were collected and the analysis of these samples was performed.

[00209] No mortality occurred and no clinical signs were observed.

[00210] The overall achieved aerosol concentrations for all groups were within 10% of the targeted concentrations gravimetrically and for both treprostini and trehalose, except for Group

2 which were significantly above the targeted concentrations (76 to 95%). Corresponding average achieved dose levels for all groups were within 5% of the targeted dose levels, except for Group 2 which was 82% above the targeted dose level. However, the dose levels were considered acceptable for the study as a clear dose differentiation between groups for each sex was achieved.

[00211] The particle size MMADs from Groups 2 to 4 were between 1.7 and 2.0 μm gravimetrically (GSD 1.90 to 2.67); for both treprostinil and trehalose, chemical particle size distribution ranged from 1.6 to 1.8 μm with the corresponding GSDs between 1.89 and 2.24. The particle size MMAD for Group 1 was 0.5 μm with a corresponding GSD of 2.60. The particle size distribution was considered respirable.

[00212] With administration of PRINT-Tre at an achieved dose level of 0.273 mg/kg, 0.762 mg/kg or 1.498 mg/kg, plasma exposure to treprostinil was generally similar in both sexes; however, exposure was slightly lower in females than males at the mid-dose level and slightly higher in females than males at the high-dose level.

[00213] Based on $\text{AUC}_{0-\text{T}_{\text{last}}}$, AUC_{INF} and C_{max} , values for both sexes, plasma exposure increased more than proportionally between the low- and mid-dose levels. But between the mid- and high-dose levels, plasma exposure increased less than proportionally for females and there was no increase in the exposure for males. The maximum mean treprostinil plasma concentration (T_{max}) was at the end of inhalation for both sexes, except for low-dose males and high-dose females, where mean T_{max} was at 1 and 0.5 hours after inhalation began, respectively.

[00214] At the low-dose level, mean treprostinil plasma concentration was similar after 0.5, 1, or 4 hours of inhalation exposure to PRINT-Tre, suggesting that steady state was achieved within the first 30 minutes of exposure. The same was true for females at the high-dose level; however, for males at the high-dose level and for both sexes at the mid-dose level, mean treprostinil plasma concentration was greater at the end of inhalation than after one hour of inhalation. When inhalation ended, treprostinil plasma concentrations declined gradually. Given the degree of individual variation, the estimated mean $\text{T}_{1/2}$ values were similar at all dose levels and ranged from 0.7 to 1.8 hours in males and 0.7 to 1.0 hours in females.

[00215] For Tre solution, with an administration at 0.785 mg/kg, plasma exposure to treprostinil was generally similar in both sexes. The maximum mean treprostinil plasma concentration (T_{max}) was at the end of inhalation. Mean treprostinil plasma concentration was similar after 0.5, 1, or 4 hours of inhalation exposure to Tre solution, suggesting that steady state was achieved within the first 30 minutes of exposure. When inhalation ended, treprostinil plasma concentrations declined gradually, with estimated mean $T_{1/2}$ values of 0.6 hours in males and 0.8 hours in females.

[00216] Administration of PRINT-Tre and Tre solution at nearly equivalent dose levels (0.76 and 0.79 mg/kg, respectively) resulted in plasma exposures to treprostinil that were greater with PRINT-Tre than with Tre solution. Specifically, mean $AUC_{0-Tlast}$ was approximately twice as high (126 versus 61 h*ng/mL, respectively) and mean C_{max} was three times as high (44 versus 16 ng/mL, respectively). As would be expected, once treprostinil entered the systemic circulation, it was cleared from plasma at a similar rate, with mean $T_{1/2}$ values of 0.7 to 1.0 hours for PRINT-Tre and 0.6 to 0.8 hours for Tre solution.

[00217] In conclusion, single inhalation administration for 4 hours of PRINT Treprostinil at a high average dose of 1.498 mg/kg/day to Sprague-Dawley rats was well tolerated as there were no test item related findings. At an equivalent dose level, plasma exposures to treprostinil was greater with PRINT-Tre than with Tre solution; specifically, mean $AUC_{0-Tlast}$ was approximately twice as great and mean C_{max} was three times as great. As would be expected, once treprostinil entered the systemic circulation, it was cleared from plasma at a similar rate regardless of how it was administered.

[00218] The objectives of the study were to:

1. Determine the pharmacokinetic (PK) profile of Treprostinil in Sprague-Dawley rats when administered as PRINT-Treprostinil (PRINT-Tre) by 4-hour inhalation at 0.15, 0.75, and 1.5 mg/kg.
2. Determine the PK profile of Treprostinil in Sprague-Dawley rats when administered as nebulized Treprostinil sodium in solution (Tre solution) by 4-hour inhalation at 0.75 mg/kg.

3. Compare the PK profiles of Treprostinil when administered as PRINT-Tre and Tre solution.

[00219] Experimental Design

[00220] The test items were administered to groups of rats by a 4-hour inhalation administration as described in the table below:

Group No.	Group Designation	Targeted Total Inhaled Dose Level of Treprostinil (mg/kg/day)	Targeted Aerosol Concentration of Treprostinil (µg/L) ^a	Targeted Aerosol Concentration of Trehalose (µg/L) ^a	No. of Animals	
					Males	Females
1	Tre Solution	0.75	5	0	6	6
2	PRINT-Tre	0.15	1	130.7	6	6
3	PRINT-Tre	0.75	5	653.5	6	6
4	PRINT-Tre	1.5	10	1306.9	6	6

^a = Target aerosol concentrations were calculated based on an estimated body weight of 0.250 kg

[00221] During and after the inhalation period, a series of 8 blood samples for pharmacokinetic evaluation were taken.

[00222] Justification for Selection of Route of Administration, Species and Dose Levels

[00223] The route of administration was chosen because it is the intended human therapeutic route.

[00224] The rat was selected because it is a rodent species recommended by various regulatory authorities. Background data are available. Also, rats were used as the test system for previous toxicity studies with Treprostinil sodium solution that supported development and approval of that product. Using rats in the current study allowed comparison with the previous studies.

[00225] The high-dose level for PRINT-Tre was the feasible dose attainable based on technical aerosol trials with the test item (Study No. 41610).

[00226] The low- and mid-dose levels for PRINT-Tre were selected on the basis of a previous pilot PK study in rats (Study No. 75670).

[00227] The dose level for Tre solution was selected to match the mid-dose level of PRINT-Tre to allow direct comparison.

- Characterization of Test Items

Content:	92.79% of Trehalose, 4% of Leucine, 2% of Tween80, 0.26% of NA Citrate, 0.24% of NaCl : 0.71% of Treprostinil
Storage Conditions:	Cool (2 to 8°C), protected from moisture (e.g., dessicant)
Handling Precautions:	Standard laboratory precautions. Handle under dry conditions (Relative Humidity \leq 23%)
Supplier:	Liquidia Technologies Inc.

Test item 2*:	Identity:	Treprostinil Sodium
	Description:	White or pale yellowish powder
	Batch No.:	TN115E010
	Expiry Date:	May 28, 2017
	Purity:	101.49%
	Storage Conditions:	Cool (2 to 8°C)
	Handling Precautions:	Standard laboratory precautions
	Supplier:	Yonsung Fine Chemicals Co., LTD

[00228] Preparation of Test Item

[00229] PRINT-Tre was used as provided by the Sponsor. A glove box under nitrogen was used for handling, aliquoting or packing of the canisters. Relative humidity (RH) inside the glove box was monitored and recorded using a hygrometer and was kept below 23% RH.

[00230] For Group 1, the treprostinil sodium was dissolved in purified water to achieve the desired formulation concentration. A representative sample (0.5mL in duplicate) was collected to verify the formulation concentration of Treprostinil in the formulation.

[00231] Treatment

[00232] Acclimatization to Exposure System

[00233] Before the animals were exposed to the aerosol of the test item, rats were accustomed to the restraint procedure over a period of 3 days. The animals were gradually accustomed to restraint in the dosing tubes used during the exposures up to the duration that was used for aerosol administrations.

[00234] Animal Exposure

Exposure system used: Flow-past rodent inhalation exposure system
Exposure method: Inhalation by nose-only exposure
Test Item type: Solution (Group 1), Dry Powder (Groups 2 to 4)
Generation method: Nebulization (Group 1) and Piston feed/rotating brush generator (Group 2 to 4)
Duration of exposure: 240 minutes

[00235] The target aerosol concentrations and dose levels were as follows:

Group No.	Group Designation	Targeted Dose Level of Treprostinil (mg/kg/day)	Targeted Aerosol Concentration of Treprostinil (µg/L) ^a	Targeted Aerosol Concentration of Trehalose (µg/L)
1	Tre solution	0.75	5	0
2	PRINT-Tre (Low Dose)	0.15	1	130.7

3	PRINT-Tre (Mid Dose)	0.75	5	653.5
4	PRINT-Tre (High Dose)	1.5	10	1306.9

a = Target aerosol concentrations were calculated based on an estimated body weight of 0.250 kg.

[00236] Estimation of Achieved Dose Levels

The target dose levels were estimated using the following formula:

$$D_L = \frac{E_c \times RMV \times T}{BW}$$

D_L = Achieved dose levels (mg / kg / day)

E_c = Actual concentration delivered to the animals (mg / L air)

RMV = Respiratory Minute Volume (L / min) according to the method of Bide, Armour and Yee 2000 J. App. Toxicol., Vol. 20: RMV (L / min) = $0.499 \times BW$ (kg)^{0.809}

T = Time, duration of daily exposure (min.)

BW = Mean body weight (kg) during exposure period.

This estimation of total inhaled dose assumed 100% deposition within the respiratory tract.

[00237] Inhalation Exposure System

[00238] The powder aerosol for Groups 2 to 4 was produced using a piston feed / rotating brush generator while the liquid aerosol for Group 1 was produced by metering the flow of the formulation to a clinical nebulizer (Sidestream). The aerosol produced was diluted as necessary to achieve the target aerosol concentration and discharged through a 40-mm diameter tube into a flow-past inhalation exposure system. The airflow rate through the exposure system was monitored and recorded manually during each aerosol generation period. Airflow to the exposure system was controlled by the absolute volume of air supplying the generation apparatus using variable area flowmeters. Control of the aerosol exhaust flow from the animal exposure system was achieved using an exhaust valve, and the overall balance of airflows in the exposure system was monitored using pressure gauges. The system provided a minimum of 1.0 L/min to

each animal exposure port and was balanced to ensure a slight positive pressure at the site of the animal exposure. This ensured that there was no dilution of the generated aerosol. An equal delivery of aerosol to each exposure position was achieved by employing a distribution network that was identical for each individual exposure position attached to the system.

[00239] Inhalation System Monitoring

[00240] Determinations of aerosol concentration, particle size distribution, oxygen concentration, relative humidity and temperature were measured on samples collected from a representative port of the exposure chamber. The sample flow rates were precisely controlled using variable area flow meters that were calibrated before use using a primary airflow calibrator. The absolute volume of each aerosol concentration sample was measured with a wet type gas meter.

[00241] Oxygen Concentration

[00242] The oxygen concentration of the generated atmosphere was measured once during each aerosol exposure. Oxygen concentrations of the exposure atmospheres were maintained between 19-23%.

[00243] Relative Humidity/Temperature

[00244] The temperature and relative humidity of the generated atmosphere were measured once during each aerosol exposure. Temperatures of the exposure atmospheres were maintained between 19-24°C.

[00245] Determination of Aerosol Concentration

[00246] At least one aerosol concentration filter sample was collected for all groups on each aerosol generation. The filter samples from Groups 2 to 4 were weighed in order to measure the gravimetric concentration of the test item in the generated aerosol. The filter samples were transferred to the analytical chemistry laboratory for chemical determination of Treprostinil and Trehalose concentrations. The filter samples for Group 1 were not weighed gravimetrically and were only transferred to the analytical laboratory for determination of Treprostinil

concentrations. The analysis in the analytical laboratory was performed using an analytical method (Study No. 41609).

[00247] Determination of the Particle Size Distribution and Mass Median Aerodynamic Diameter (MMAD)

[00248] The distribution of particle size in the generated aerosols was measured once for Groups 1 to 4 by collecting samples into a 7-Stage Mercer Cascade Impactor. All sample substrates obtained from Groups 2 to 4 were weighed gravimetrically and then transferred to the analytical chemistry laboratory for chemical determination of particle size of aerosolized Treprostinil and Trehalose. All sample substrates obtained from Group 1 were only transferred to the analytical laboratory for chemical determination of particle size of aerosolized Treprostinil. The analysis in the analytical laboratory was performed using an analytical method (Study No. 41609).

[00249] The MMAD and the Geometric Standard Deviation (GSD) were calculated based on the results obtained from the impactor using a log-probit transformation.

[00250] Reporting of Analytical Results

[00251] The analytical report containing the results from the filter and particle size distribution sample analyses were prepared. Any samples not employed in the primary analysis or any remaining sample from the primary analysis were retained until it was determined by the analyst and Study Director that it was not be required for confirmatory analysis. These samples were discarded and their disposition recorded in the raw data.

[00252] IN-LIFE OBSERVATIONS

[00253] Mortality

[00254] Mortality checks were performed at least once a day during all phases of the study.

[00255] Clinical Observations

[00256] Cage-side clinical signs (ill health, behavioral changes etc.) were recorded at least once daily during all phases of the study, except on detailed clinical examination days, where the cage-side clinical signs were replaced by a DCE.

[00257] A detailed clinical examination of each rat was performed on arrival as part of the health status, as well as on Day 1, prior to dosing.

[00258] Body Weights

[00259] Body weights were recorded for all animals once at arrival as per health status, once prior to group assignment and on Day 1 (prior to dosing).

[00260] Pharmacokinetics

[00261] A series of 8 blood samples (approximately 0.3 mL each) was collected 30 minutes and 1 hour after exposure began, immediately after exposure ended (IPE), and again at 5, 15, 30, 75 and 105 minutes post-dosing as per the table below. Thus a total blood volume of 1.2 mL was taken from each rat during the course of the study. For this purpose, each rat (unanesthetized) was bled by jugular venipuncture and the samples were collected into tubes containing the anticoagulant, K₂EDTA. Tubes were placed on wet ice pending processing.

Group Number	Number of animals/sex	Toxicokinetic time point							
		30 min post start	1 hour post start	IPE	5 min post end	15 min post end	30 min post end	75 min post end	105 min post end
1	3 +	√		√		√		√	
	3 #		√		√		√		√
2	3 +	√		√		√		√	
	3 #		√		√		√		√
3	3 +	√		√		√		√	
	3 #		√		√		√		√
4	3 +	√		√		√		√	
	3 #		√		√		√		√

+ animals with the lowest identification numbers

animals with the highest identification numbers

[00262] Following collection, the samples were centrifuged (2500 rpm for 10 minutes at approximately 4°C) and the resulting plasma was recovered and stored frozen ($\leq -60^{\circ}\text{C}$) in labeled tubes.

[00263] Deviations to the pharmacokinetic time points were noted in the raw data and were made available with the samples. The location of blood withdrawal was noted in the raw data.

[00264] The plasma analysis was performed and the bioanalytical data was prepared for inclusion in the final report.

[00265] The pharmacokinetic parameters were calculated and the non-compartmental analysis of PRINT-Tre and Tre solution treprostinil concentrations in plasma was performed by using the Phoenix WinNonlin 6.3 software.

[00266] The following configuration was used for the analysis:

Sampling Method:	Sparse
AUC Calculation Method:	Linear Trapezoidal with Linear Interpolation
Lambda Z (λ_z) Method:	Best fit for λ_z , Log regression
Weighting (λ_z calculation):	Uniform

[00267] Pharmacokinetic parameters (including abbreviation and description for each parameter) were described in the following table:

Parameters	Abbreviation	Unit*
Area under the plasma drug concentration-time curve from the time of dosing to the last quantifiable concentration	$AUC_{0-T_{last}}$	$\mu\text{g}\cdot\text{hr}/\text{mL}$
Area under the plasma drug concentration-time curve from the time of dosing extrapolated to infinity	AUC_{INF}	$\mu\text{g}\cdot\text{hr}/\text{mL}$
Terminal elimination half-life	$T_{1/2}$	hr
The maximum plasma concentration	C_{max}	$\mu\text{g}/\text{mL}$
Time to maximum plasma concentration	T_{max}	hr

[00268] Data Evaluation and Statistics

[00269] Numeric and non-numeric data obtained during the study were reported only as individual values.

[00270] RESULTS**[00271] Formulation Analysis**

[00272] Formulation concentration for Group 1 was as follows:

Group No.	Average Targeted Concentration (mg/mL)	Average Measured Concentration (mg/mL)	% of Targeted Concentration
1	0.50	0.492	98.4

[00273] The formulation concentration for Group 1 was within 2% of the targeted concentration therefore the formulation concentration was considered acceptable for the study.

[00274] Aerosol Concentrations

[00275] Achieved gravimetric test atmosphere concentrations were as follows:

Group No.	Targeted Aerosol Concentration (mg/L)	Achieved Mean Aerosol Concentration (mg/L)	Coefficient of Variation (%)	% of Target
2	0.156	0.283	55.5	181.4
3	0.781	0.814	16.3	104.2
4	1.563	1.548	21.9	99.0

[00276] Achieved chemical test atmosphere concentrations for treprostinil were as follows:

Group No.	Targeted Aerosol Concentration (µg/L)	Achieved Mean Aerosol Concentration (µg/L)	Coefficient of Variation (%)	% of Target
1	5	5.07	3.6	101.4
2	1	1.76	55.2	176.3
3	5	4.95	19.8	99.1
4	10	9.73	22.3	97.3

[00277] Achieved chemical test atmosphere concentrations for trehalose were as follows:

Group No.	Targeted Aerosol Concentration (µg/L)	Achieved Mean Aerosol Concentration (µg/L)	Coefficient of Variation (%)	% of Target
2	130.7	254.84	54.4	195.0
3	653.5	719.53	20.5	110.1
4	1306.9	1394.33	23.2	106.7

[00278] The overall achieved aerosol concentrations for all groups were within 10% of the targeted concentrations gravimetrically and for both treprostinil and trehalose, except for Group 2 which were significantly above the targeted concentrations (76% and 95% for treprostinil and trehalose, respectively). The generated atmospheres were considered stable over the treatment period except for Group 2 (CV % ~54%). However, the overall aerosol concentrations were still considered acceptable for the study as there was a significant difference in aerosol concentration between groups.

[00279] Achieved Dose Levels

[00280] Overall achieved doses for treprostinil are presented below:

Group No.	Targeted Dose Level (mg/kg/day)	Duration of Exposure (min)	Sex	Body Weight (kg)	Estimated Achieved Doses (mg/kg/day)	% from Targeted Dose Level
1	0.75	240	Male	0.308	0.760	101.4
			Female	0.212	0.817	108.9
			<i>Combined</i>	<i>0.260</i>	<i>0.785</i>	<i>104.7</i>
2	0.15	240	Male	0.301	0.265	176.7
			Female	0.211	0.284	189.1
			<i>Combined</i>	<i>0.256</i>	<i>0.273</i>	<i>182.3</i>
3	0.75	240	Male	0.321	0.737	98.2
			Female	0.215	0.795	106.0
			<i>Combined</i>	<i>0.268</i>	<i>0.762</i>	<i>101.6</i>
4	1.5	240	Male	0.317	1.451	96.7
			Female	0.219	1.557	103.8
			<i>Combined</i>	<i>0.268</i>	<i>1.498</i>	<i>99.9</i>

[00281] Average achieved dose levels for all groups were within 5% of the targeted dose levels, except for Group 2 which was 82% above the targeted dose level. However, the dose levels were considered acceptable for the study as a clear dose differentiation between groups for each sex was achieved.

[00282] Particle Size Distribution

[00283] The average gravimetric particle size distribution measurement data were as follows:

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Group No.	Cumulative % Less Than Stated Effective Cut-Off Diameter (µm)								Mean		% below 4 µm
	4.60	3.00	2.10	1.60	1.10	0.70	0.33	0.00	MMAD (µm)	GSD	
2	87.9	80.0	61.0	31.2	21.8	16.2	9.1	0.0	1.7	2.67	80
3	90.7	85.0	66.9	24.9	14.8	9.0	3.0	0.0	1.8	2.12	85
4	91.7	84.0	61.6	23.5	8.1	4.3	0.8	0.0	2.0	1.90	86

MMAD=Mass median aerodynamic diameter

GSD=Geometric standard deviation.

[00284] The average chemical determination of particle size distribution for treprostinil were as follows:

Group No.	Cumulative % Less Than Stated Effective Cut-Off Diameter (µm)								Mean		% below 4 µm
	4.60	3.00	2.10	1.60	1.10	0.70	0.33	0.00	MMAD (µm)	GSD	
1	95.9	95.7	95.4	95.1	85.1	50.1	22.0	0.0	0.5	2.60	98
2	94.0	86.3	64.4	29.3	19.8	14.1	6.1	0.0	1.6	2.24	87
3	95.3	90.3	71.5	25.9	15.2	9.3	2.7	0.0	1.6	1.97	90
4	94.1	88.4	64.3	23.9	8.2	4.4	1.5	0.0	1.8	1.89	88

MMAD=Mass median aerodynamic diameter

GSD=Geometric standard deviation.

[00285] The average chemical determination of particle size distribution for trehalose were as follows:

Group No.	Cumulative % Less Than Stated Effective Cut-Off Diameter (µm)								Mean		% below 4 µm
	4.60	3.00	2.10	1.60	1.10	0.70	0.33	0.00	MMAD (µm)	GSD	
2	94.3	86.7	63.8	26.4	16.8	14.1	6.1	0.0	1.6	2.22	87
3	96.0	92.0	72.3	22.2	12.0	8.0	4.0	0.0	1.6	1.97	90
4	95.7	91.4	68.0	27.9	12.8	8.6	4.3	0.0	1.6	2.00	90

MMAD=Mass median aerodynamic diameter

GSD=Geometric standard deviation.

[00286] The particle size distribution was considered respirable for this study as the MMADs were below 4 µm and the GSD were within 1.5 and 3.

[00287] Exposure Chamber Conditions

[00288] Exposure chamber conditions from the reported aerosol concentration exposures are summarized below.

Group No.	Humidity (%RH)	Temperature (°C)	Oxygen Concentration (%)
1	58.5	21.0	20.9
2	35.1	21.6	20.9
3	39.0	21.5	20.9
4	39.4	21.2	20.9

[00289] Exposure atmosphere oxygen concentrations, temperature and relative humidity ranges were considered acceptable on all occasions.

[00290] Mortality

[00291] There were no mortalities during the study.

[00292] Clinical Signs

[00293] There were no clinical signs observed during the study.

[00294] Body Weight

[00295] Body weights were performed for dose level calculation purposes.

[00296] Pharmacokinetics

[00297] With administration of PRINT-Tre at an achieved dose level of 0.273 mg/kg, 0.762 mg/kg or 1.498 mg/kg, plasma exposure to treprostinil was generally similar in both sexes; however, exposure was slightly lower in females than males at the mid-dose level and slightly higher in females than males at the high-dose level.

[00298] Based on $AUC_{0-T_{last}}$, AUC_{INF} and C_{max} , values for both sexes, plasma exposure increased more than proportionally between the low- and mid-dose levels. But between the mid- and high-dose levels, plasma exposure increased less than proportionally for females and there was no increase in the exposure for males. The maximum mean treprostinil plasma concentration (T_{max}) was at the end of inhalation for both sexes, except for low-dose males and high-dose females, where mean T_{max} was at 1 and 0.5 hours after inhalation began, respectively.

[00299] At the low-dose level, mean treprostinil plasma concentration was similar after 0.5, 1, or 4 hours of inhalation exposure to PRINT-Tre, suggesting that steady state was achieved within the first 30 minutes of exposure. The same was true for females at the high-dose level; however, for males at the high-dose level and for both sexes at the mid-dose level, mean treprostinil plasma concentration was greater at the end of inhalation than after one hour of inhalation. These data are summarized below.

	Males			Females		
Dose (mg/kg) =	0.273	0.762	1.498	0.273	0.762	1.498
0.5 hours of inhalation	6.1	22	26	4.2	18	44
1 hour of inhalation	7.2	21	27	5.1	19	35
4 hours of inhalation	5.4	54*	44^	5.4	33**	44

*Individual values were 33, 63, and 67 ng/mL

^Individual values were 34, 48, and 50 ng/mL

**Individual values were 22, 27, and 49 ng/mL

[00300] When inhalation ended, treprostinil plasma concentrations declined gradually. Given the degree of individual variation, the estimated mean $T_{1/2}$ values were similar at all dose levels and ranged from 0.7 to 1.8 hours in males and 0.7 to 1.0 hours in females.

[00301] For Tre solution, with an administration at 0.785 mg/kg, plasma exposure to treprostinil was generally similar in both sexes.

[00302] The maximum mean treprostinil plasma concentration (T_{max}) was at the end of inhalation. Mean treprostinil plasma concentration was similar after 0.5, 1, or 4 hours of inhalation exposure to Tre solution, suggesting that steady state was achieved within the first 30 minutes of exposure. These data are summarized below.

	Males	Females
0.5 hours of inhalation	17	12
1 hour of inhalation	11	14
4 hours of inhalation	16	16

[00303] When inhalation ended, treprostinil plasma concentrations declined gradually, with estimated mean $T_{1/2}$ values of 0.6 hours in males and 0.8 hours in females.

[00304] Administration of PRINT-Tre and Tre solution at nearly equivalent dose levels (0.76 and 0.79 mg/kg, respectively) resulted in plasma exposures to treprostinil that were greater with PRINT-Tre than with Tre solution. Specifically, mean $AUC_{0-T_{last}}$ was approximately twice as high (126 versus 61 h*ng/mL, respectively) and mean C_{max} was three times as high (44 versus 16 ng/mL, respectively). As would be expected, once treprostinil entered the systemic circulation, it was cleared from plasma at a similar rate, with mean $T_{1/2}$ values of 0.7 to 1.0 hours for PRINT-Tre and 0.6 to 0.8 hours for Tre solution.

[00305] CONCLUSION

[00306] Single inhalation administration for 4 hours of PRINT Treprostinil at a high average dose of 1.498 mg/kg/day to Sprague-Dawley rats was well tolerated as there were no test item related findings. At an equivalent dose level, plasma exposures to treprostinil was greater with PRINT-Tre than with Tre solution; specifically, mean $AUC_{0-T_{last}}$ was approximately twice as great and mean C_{max} was three times as great. As would be expected, once treprostinil entered the systemic circulation, it was cleared from plasma at a similar rate regardless of how it was administered.

[00307] Non-GLP, 7-day, repeat-dose, range-finding (DRF), inhalation study with LIQ861 in rats (Study 75654)

[00308] Results from the completed comparative PK study will be used to select dose levels to be tested in this DRF study, which will evaluate local toxicity in the respiratory tract as well as systemic treprostinil toxicity. Results will be used to select appropriate dose levels for a 2-week GLP repeat-dose toxicology study in rats.

[00309] Summary: Study 75654

[00310] The objectives of the study were to evaluate the toxicity of the test item, PRINT Treprostinil, and the excipients that make up the control item, PRINT Placebo, when administered to Sprague-Dawley rats by nose-only inhalation for 4 hours a day for 7 days. Results were used to help select dose levels for a subsequent 14-day GLP inhalation toxicology study.

[00311] Groups of 6 rats (3/sex) were exposed by 4-hour inhalation daily for 7 days to air, PRINT Placebo, or PRINT Treprostinil at treprostinil dose levels of approximately 170, 680, or 1370 $\mu\text{g/kg}$, as described in the table below:

Group No.	Group Designation	Mean Dose Levels and Concentrations ^a				
		Treprostiniil		Trehalose		Leucine
		Dose Level (µg/kg/day)	Aerosol Conc. (µg/L)	Dose Level (mg/kg/day)	Aerosol Conc. (µg/L)	Dose Level (mg/kg/day) ^b
1	Air Control	0	0	0	0	0
2	Placebo Control ^b	0	0	281.2	1832.13	12.0
3	PRINT-Tre (Low Dose)	170	1.10	33.1	216.30	1.3
4	PRINT-Tre (Mid Dose)	680	4.44	133.5	869.99	5.1
5	PRINT-Tre (High Dose)	1370	8.94	266.6	1735.84	10.3

a = Based on the mean body weight of each group during the dosing period.

b = Calculated with a content of 4% of Leucine in PRINT Treprostiniil and PRINT Placebo and using Trehalose percentage of 93.5% in PRINT Placebo for Group 2 and Treprostiniil percentage of 0.53% in PRINT Treprostiniil for Groups 3 to 5.

[00312] The particle size MMADs from Groups 2 to 5 were between 1.3 and 2.0 µm gravimetrically (GSD 1.96 to 2.46); for both treprostiniil and trehalose, chemical particle size distribution ranged from 1.3 to 2.1 µm with the corresponding GSDs between 1.87 and 1.95. No mortality occurred. No clinical signs were observed while coagulation, clinical chemistry and urinalysis parameters were unaffected and no test item-related findings were seen macroscopically.

[00313] Rats tolerated daily administration of PRINT Placebo or PRINT-Tre at up to 1.37 mg/kg/day by 4-hour inhalation for 7 days.

[00314] Introduction

[00315] The objectives of the study were to:

1. Evaluate the toxicity of the test item, PRINT Treprostiniil, when administered to Sprague-Dawley rats by nose-only inhalation for 4 hours a day for 7 days.

2. Evaluate the toxicity of the excipients that make up the control item, PRINT Placebo, when administered to Sprague-Dawley rats by nose-only inhalation for 4 hours a day for 7 days.
3. Determine the dose levels of PRINT Treprostinil for the following 14-day GLP inhalation toxicology study from the results of this dose range-finding study.

[00316] Experimental Design**[00317] Synopsis**

[00318] The test and control items were administered to groups of 6 rats (3/sex) by 4-hour inhalation daily for 7 days, as described in the table below. The first day of dosing was designated as Day 1.

Group No.	Test Material	Targeted Aerosol Concentration (µg/L)		Targeted Dose Level (mg/kg/day)		Leucine Dose Level (mg/kg/day) ^c
		Treprostinil	Trehalose	Treprostinil ^a	Trehalose ^b	
1	Air Control	0	0	0	0	0
2	PRINT Placebo ^b	0	1684.6	0	262.9	11.2
3	PRINT-Tre (Low Dose)	1	175.2	0.15	26.3	1.1
4	PRINT-Tre (Mid Dose)	5	876.2	0.75	131.4	5.7
5	PRINT-Tre (High Dose)	10	1752.5	1.5	262.9	11.3

a = Target aerosol concentrations were calculated based on an estimated body weight of 0.250 kg

b = The target dose level for the placebo control was the same dose level as the high dose group (Group 5)

c = Calculated with a content of 4% of Leucine in PRINT Treprostinil and PRINT Placebo (using Trehalose percentage of 93.5% in PRINT Placebo for Group 2 and Treprostinil percentage of 0.53% in PRINT Treprostinil for Groups 3 to 5)

[00319] The high-dose level for PRINT-Tre was the feasible dose attainable based on technical aerosol trials with the test item. (Study No. 41610).

[00320] The low- and mid-dose levels for PRINT-Tre were selected on the basis of a previous PK study in rats (Study No. 75658).

[00321] Test and Control Item Information

[00322] Test Item Action

[00323] Treprostinil, the active ingredient in PRINT-Tre, is a prostacyclin compound approved for treatment of pulmonary arterial hypertension.

[00324] Characterization of Test Item

Content: 92.97% of Trehalose, 4% of Leucine, 2% of Tween80, 0.27% of Sodium Citrate Dihydrate, 0.23% of Sodium Chloride : 0.53% of Treprostinil sodium

Storage Conditions: Cool (2 to 8°C), protected from moisture (e.g., desiccant)

Handling Precautions: Standard laboratory precautions. Handled under dry conditions (relative humidity \leq 23%)

Supplier: Liquidia Technologies Inc.

[00325] Characterization of Placebo Control Item

Content: -LKI-1R-983-3: 93.53% of Trehalose, 4% of Leucine, 2% of Tween80, 0.24% of Sodium Citrate Dihydrate, 0.23% of Sodium Chloride

-LKI-1R-983-27: 93.5% of Trehalose, 4% of Leucine, 2% of Tween80, 0.27% of Sodium Citrate Dihydrate, 0.23% of Sodium Chloride

Storage Conditions: Cool (2 to 8°C) , protected from moisture (e.g., desiccant)

Handling Precautions: Standard laboratory precautions. Handled under dry conditions (relative humidity \leq 23%)

Supplier: Liquidia Technologies Inc.

[00326] Characterization of Air Control

Description: Medical Grade Air (NQ 5710-500/2000)

Supplied By: Kaeser SM-11 Air Compressor

[00327] Preparation of Test and Control Items

[00328] PRINT-Tre and PRINT Placebo were used as provided by the Sponsor. A glove box under nitrogen was used for handling, aliquoting or packing of the canisters. Relative humidity (RH) inside the glove box was monitored and recorded using a hygrometer and was kept below 23% RH.

[00329] Treatment

[00330] Acclimatization to Exposure System

[00331] Before the rats were presented to exposure atmosphere, rats were accustomed to the restraint procedure over a period of 3 days. The animals were gradually accustomed to restraint in the dosing tubes used during the exposures up to the duration that was used for aerosol administrations.

[00332] Animal Exposure

Exposure system used: Flow-past rodent inhalation exposure system

Exposure method: Inhalation by nose-only exposure

Test and Control Item type: Air (Group 1), Dry Powder (Groups 2 to 5)

Generation method: Piston feed/rotating brush generator (Groups 2 to 5)

Duration of exposure: 240 minutes

[00333] The target aerosol concentrations and dose levels were as follows:

Group No.	Group Designation	Targeted Total Inhaled Dose Level of Treprostinil (mg/kg/day) ^a	Targeted Aerosol Concentration of Treprostinil (µg/L)	Targeted Total Inhaled Dose Level of Trehalose (mg/kg/day) ^a	Targeted Aerosol Concentration of Trehalose (µg/L)	Estimated Total Inhaled Dose Level of Leucine (mg/kg/day) ^c
1	Air Control	0	0	0	0	0
2	Placebo Control ^b	0	0	262.9	1684.6	11.2
3	PRINT-Tre (Low Dose)	0.15	1	26.3	175.2	1.1
4	PRINT-Tre (Mid Dose)	0.75	5	131.4	876.2	5.7
5	PRINT-Tre (High Dose)	1.5	10	262.9	1752.5	11.3

a = Target aerosol concentrations were calculated based on an estimated body weight of 0.250 kg

b = The target dose level for the placebo control was the dose level as the high dose group (Group 5)

c = Calculated with a content of 4% of Leucine in PRINT Treprostinil and PRINT Placebo (using Trehalose percentage of 93.5% in PRINT Placebo for Group 2 and Treprostinil percentage of 0.53% in PRINT Treprostinil for Groups 3 to 5)

[00334] Estimation of Achieved Dose Levels

The target dose levels were estimated using the following formula:

$$D_L = \frac{E_c \times RMV \times T}{BW}$$

D_L = Achieved dose levels (mg / kg / day)

E_c = Actual concentration delivered to the animals (mg / L air)

RMV = Respiratory Minute Volume (L / min) according to the method of Bide, Armour and Yee. J. App. Toxicol., Vol. 20, 2000: RMV (L / min) = $0.499 \times BW$ (kg)^{0.809}

T = Time, duration of daily exposure (min.)

BW = Mean body weight (kg) during exposure period.

This estimation of total inhaled dose assumed 100% deposition within the respiratory tract.

[00335] Inhalation Exposure System

[00336] The powder aerosol for Groups 2 to 5 was produced using a piston feed / rotating brush generator. The aerosol produced was diluted as necessary to achieve the target aerosol concentration and discharged through a 40-mm diameter tube into a flow-past inhalation exposure system. The airflow rate through the exposure system was monitored and recorded manually during each aerosol generation period. Airflow to the exposure system was controlled by the absolute volume of air supplying the generation apparatus using variable area flowmeters. Control of the aerosol exhaust flow from the animal exposure system was achieved using an exhaust valve, and the overall balance of airflows in the exposure system was monitored using pressure gauges. The system provided a minimum of 1.0 L/min to each animal exposure port and was balanced to ensure a slight positive pressure at the site of the animal exposure. This ensured that there was no dilution of the generated aerosol. An equal delivery of aerosol to each exposure position was achieved by employing a distribution network that was identical for each individual exposure position attached to the system.

[00337] Inhalation System Monitoring

[00338] Determinations of aerosol concentration, particle size distribution, oxygen concentration, relative humidity and temperature were measured on samples collected from a representative port of the exposure chamber, with a collection sample flow-rate of 1 L/min. The sample flow rates were precisely controlled using variable area flow meters that were calibrated before use using a primary airflow calibrator. The absolute volume of each aerosol concentration sample was measured with a wet type gas meter.

[00339] Oxygen Concentration

[00340] The oxygen concentration of the generated atmosphere was measured once during each aerosol exposure. Oxygen concentrations of the exposure atmospheres were maintained between 19-23%.

[00341] Relative Humidity/Temperature

[00342] The temperature and relative humidity of the generated atmosphere were measured once during each aerosol exposure. Temperatures of the exposure atmospheres were maintained between 19-24°C.

[00343] Determination of Aerosol Concentration

[00344] At least one aerosol concentration filter sample was collected for all groups on each aerosol generation. The filter samples from Groups 3 to 5 were weighed in order to measure the gravimetric concentration of the test item in the generated aerosol. The filter samples were transferred to the analytical chemistry laboratory for chemical determination of Treprostinil and Trehalose concentrations. The filter samples from Group 2 were weighed in order to measure the gravimetric concentration of the control item in the generated aerosol. The filter samples were transferred to the analytical chemistry laboratory for chemical determination of Trehalose concentration and to confirm the absence of Treprostinil. The filter samples for Group 1 were not weighed gravimetrically and were only transferred to the analytical laboratory to confirm the absence of Treprostinil and Trehalose. The analysis in the analytical laboratory was performed using an analytical method (Study No. 41609 and 41635).

[00345] Determination of Aerosol Homogeneity

[00346] At least once during the study, atmosphere homogeneity in the exposure system was tested by collecting multiple aerosol samples from the top, middle and bottom tiers of the exposure system of Groups 2 to 5.

[00347] Determination of the Particle Size Distribution and Mass Median Aerodynamic Diameter (MMAD)

[00348] The distribution of particle size in the generated aerosols was measured at least once for Groups 2 to 5 by collecting samples into a 7-Stage Mercer Cascade Impactor. All sample substrates obtained from Groups 3 to 5 were weighed gravimetrically and then transferred to the analytical chemistry laboratory for chemical determination of particle size of aerosolized Treprostinil and Trehalose. All sample substrates obtained from Group 2 were weighed gravimetrically and then transferred to the analytical laboratory for determination of particle size of aerosolized Trehalose. The analysis in the analytical laboratory was performed using an analytical method (Study No. 41609 and 41635).

[00349] The MMAD and the Geometric Standard Deviation (GSD) were calculated based on the results obtained from the impactor using a log-probit transformation.

[00350] Reporting of Analytical Results

[00351] The analytical report containing the results from the filter and particle size distribution sample analyses were prepared. Any samples not employed in the primary analysis or any remaining sample from the primary analysis were retained until it was determined by the analyst and Study Director that it was not required for confirmatory analysis. These samples were then discarded and their disposition was recorded in the raw data.

[00352] Standard Operating Procedures

[00353] All procedures, were performed in accordance with the Standard Operating Procedures and these were kept on file. Deviations to the Standard Operating Procedures were documented in the raw data.

[00354] RESULTS**[00355] Inhalation System Monitoring**

[00356] Oxygen Concentration, Temperature, and Relative Humidity

[00357] Exposure chamber conditions from the reported aerosol concentration exposures are summarized below.

Group Number	Humidity (%RH)	Temperature (°C)	Oxygen Concentration (%)
	Average	Average	Average
1	28.6	20.4	20.9
2	39.6	21.2	20.9
3	35.6	21.6	20.9
4	26.2	21.1	20.9
5	31.1	20.8	20.9

[00358] Exposure atmosphere oxygen concentration, temperature and relative humidity were considered acceptable throughout the study.

[00359] Aerosol Concentrations

[00360] Achieved gravimetric test atmosphere concentrations were as follows:

Group No.	Targeted Aerosol Concentration (mg/L)	Achieved Mean Aerosol Concentration (mg/L)	Coefficient of Variation (%)	% of Target
2	2.000*	1.966	34.7	98.3
3	0.200*	0.231	21.4	115.5
4	1.000*	0.928	20.5	92.8
5	2.000*	1.848	26.0	92.4

* Target aerosol concentrations were 0.140mg/L for Group 3, 0.700mg/L for Group 4 and 1.400mg/L for Groups 2 and 5 for the first 2 days of exposure.

[00361] Achieved test atmosphere concentrations for treprostinil were as follows:

Group No.	Targeted Aerosol Concentration (µg/L)	Achieved Mean Aerosol Concentration (µg/L)	Coefficient of Variation (%)	% of Target
3	1.0	1.10	22.1	110.0
4	5.0	4.44	21.0	88.8
5	10.0	8.94	28.1	89.4

[00362] Achieved test atmosphere concentrations for trehalose were as follows:

Group No.	Targeted Aerosol Concentration (µg/L)	Achieved Mean Aerosol Concentration (µg/L)	Coefficient of Variation (%)	% of Target
2	1684.6	1832.13	36.4	108.8
3	175.2	216.30	22.1	123.5
4	876.2	869.99	21.2	99.3
5	1752.5	1735.84	29.4	99.0

[00363] The overall achieved aerosol concentrations for all groups were within 20% of the targeted concentrations gravimetrically and for both treprostinil and trehalose, except for Group

3 for trehalose which was 23.5% greater than the targeted concentration. The generated atmospheres were considered stable over the treatment period even if all % CV were all above 20% as this was due the wrong targeted gravimetric concentrations being applied for the first 2 days of dosing. The overall aerosol concentrations were still considered acceptable for the study as there was a significant difference in aerosol concentration between groups.

[00364] Aerosol Homogeneity

[00365] Achieved gravimetric test atmosphere homogeneity concentrations were as follows:

Group No.	Aerosol Concentration of Top Tier (mg/L)	Aerosol Concentration of Middle Tier (mg/L)	Aerosol Concentration of Bottom Tier (mg/L)	CV (%)
2	1.061	1.029	1.078	2.4
3	0.134	0.136	0.126	4.0
4	0.810	0.877	0.845	4.0
5	1.225	1.263	1.280	2.2

[00366] Achieved test atmosphere homogeneity concentrations for treprostinil were as follows:

Group No.	Aerosol Concentration of Top Tier (µg/L)	Aerosol Concentration of Middle Tier (µg/L)	Aerosol Concentration of Bottom Tier (µg/L)	CV (%)
3	0.63	0.64	0.59	4.3
4	3.90	4.16	4.04	3.2
5	5.73	6.03	6.12	3.4

[00367] Achieved test atmosphere homogeneity concentrations for trehalose were as follows:

Group No.	Aerosol Concentration of Top Tier (µg/L)	Aerosol Concentration of Middle Tier (µg/L)	Aerosol Concentration of Bottom Tier (µg/L)	CV (%)
2	916.21	888.61	919.90	1.9
3	113.82	111.38	102.88	5.3
4	774.67	887.67	780.97	7.8
5	1091.32	1153.45	1160.14	3.3

[00368] Chamber homogeneity of the aerosol concentrations were considered acceptable since the coefficient of variance of aerosol concentration between samples was not greater than 20%.

[00369] Particle Size Distribution

[00370] The average gravimetric particle size distribution measurement data were as follows:

Group No.	Cumulative % Less Than Stated Effective Cut-Off Diameter (µm)								Mean		% below 4 µm
	4.60	3.00	2.10	1.60	1.10	0.70	0.33	0.00	MMAD (µm)	GSD	
2	89.1	81.8	51.3	19.3	11.6	9.4	7.9	0.0	2.0	2.46	78
3	97.9	95.0	79.6	35.5	21.1	15.1	5.7	0.0	1.3	1.96	94
4	95.5	89.4	60.3	24.1	13.4	9.0	4.8	0.0	1.7	2.07	88
5	96.9	92.3	63.1	28.2	15.7	8.5	4.8	0.0	1.6	1.99	91

MMAD=Mass median aerodynamic diameter

GSD=Geometric standard deviation.

[00371] The chemical determinations of particle size distribution for treprostinil were as follows:

Group No.	Cumulative % Less Than Stated Effective Cut-Off Diameter (µm)								Mean		% below 4 µm
	4.60	3.00	2.10	1.60	1.10	0.70	0.33	0.00	MMAD (µm)	GSD	
3	98.8	95.7	80.3	35.2	20.2	14.2	5.0	0.0	1.3	1.88	96
4	96.3	90.1	59.9	22.2	11.1	6.9	2.9	0.0	1.7	1.95	89
5	97.2	92.8	63.3	26.7	13.6	6.4	2.8	0.0	1.6	1.89	92

MMAD=Mass median aerodynamic diameter

GSD=Geometric standard deviation.

[00372] The chemical determinations of particle size distribution for trehalose were as follows:

Group No.	Cumulative % Less Than Stated Effective Cut-Off Diameter (µm)								Mean		% below 4 µm
	4.60	3.00	2.10	1.60	1.10	0.70	0.33	0.00	MMAD (µm)	GSD	
2	89.3	85.2	52.1	17.7	8.1	4.0	0.0	0.0	2.1	1.74	87
3	96.6	93.3	77.4	31.0	15.4	12.0	3.4	0.0	1.5	1.94	93
4	97.3	90.9	59.3	19.9	8.0	5.3	2.7	0.0	1.8	1.88	90
5	97.2	94.4	62.6	25.0	12.1	5.6	2.8	0.0	1.6	1.87	92

MMAD=Mass median aerodynamic diameter

GSD=Geometric standard deviation.

[00373] The particle size distribution was considered respirable for this study as all MMADs were below 4 µm and the GSDs were within 1.5 and 3.

[00374] Estimation of Achieved Dose Levels

[00375] Overall achieved doses for treprostinil are presented below:

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Group No.	Targeted Dose Level (mg/kg/day)	Duration of Exposure (min)	Sex	Body Weight (kg)	Estimated Achieved Doses (mg/kg/day)	% of Targeted Dose Level
3	0.15	240	Male	0.324	0.16	106.7
			Female	0.227	0.17	113.3
			<i>Combined</i>	<i>0.276</i>	<i>0.17</i>	<i>113.3</i>
4	0.75	240	Male	0.316	0.66	88.0
			Female	0.229	0.70	93.3
			<i>Combined</i>	<i>0.273</i>	<i>0.68</i>	<i>90.7</i>
5	1.5	240	Male	0.315	1.33	88.7
			Female	0.228	1.42	94.7
			<i>Combined</i>	<i>0.272</i>	<i>1.37</i>	<i>91.3</i>

[00376] Overall achieved doses for trehalose are presented below:

Group No.	Targeted Dose Level (mg/kg/day)	Duration of Exposure (min)	Sex	Body Weight (kg)	Estimated Achieved Doses (mg/kg/day)	% of Targeted Dose Level
2	262.9	240	Male	0.316	273.4	104.0
			Female	0.229	290.8	110.6
			<i>Combined</i>	<i>0.273</i>	<i>281.2</i>	<i>107.0</i>
3	26.3	240	Male	0.324	32.1	122.1
			Female	0.227	34.4	130.8
			<i>Combined</i>	<i>0.276</i>	<i>33.1</i>	<i>125.9</i>
4	131.4	240	Male	0.316	129.8	98.8
			Female	0.229	138.1	105.1
			<i>Combined</i>	<i>0.273</i>	<i>133.5</i>	<i>101.6</i>
5	262.9	240	Male	0.315	259.2	98.6
			Female	0.228	275.7	104.9
			<i>Combined</i>	<i>0.272</i>	<i>266.6</i>	<i>101.4</i>

[00377] Overall achieved doses for leucine are presented below:

Group No.	Targeted Dose Level (mg/kg/day)	Duration of Exposure (min)	Sex	Body Weight (kg)	Estimated Achieved Doses ^a (mg/kg/day)	% of Targeted Dose Level
2	11.2	240	Male	0.316	11.7	104.5
			Female	0.229	12.4	110.7
			<i>Combined</i>	<i>0.273</i>	<i>12.0</i>	<i>107.1</i>
3	1.1	240	Male	0.324	1.2	109.1
			Female	0.227	1.3	118.2
			<i>Combined</i>	<i>0.276</i>	<i>1.3</i>	<i>118.2</i>
4	5.7	240	Male	0.316	5.0	87.7
			Female	0.229	5.3	93.0
			<i>Combined</i>	<i>0.273</i>	<i>5.1</i>	<i>89.5</i>
5	11.3	240	Male	0.315	10.0	88.5
			Female	0.228	10.7	94.7
			<i>Combined</i>	<i>0.272</i>	<i>10.3</i>	<i>91.2</i>

a = Calculated with a content of 4% of Leucine in PRINT-Tre and PRINT Placebo (using Trehalose percentage of 93.5% in PRINT Placebo for Group 2 and Treprostinil percentage of 0.53% in PRINT-Tre for Groups 3 to 5)

[00378] Average achieved dose levels for all groups were within 20% of the targeted dose levels, except for Group 3 for trehalose which was 26% above the targeted dose level; however, the dose levels were considered acceptable for the study as a clear dose differentiation between groups for each sex was achieved.

[00379] Mortality

[00380] There were no mortalities during the study.

[00381] Clinical Signs

[00382] There were no clinical signs observed during the study.

[00383] Body Weight

[00384] The only differences in body weight or weight gain potentially related to administration of the test or control item were slightly less growth (weight gain) in males given PRINT-Tre at 0.68 mg/kg/day and in both sexes given to PRINT-Tre at 1.37 mg/kg/day, relative to the air control group. The pattern of differences implicates the active ingredient treprostinil, not one of the excipients in PRINT-Tre.

[00385] These data are summarized in the table below, with differences potentially related to treprostinil in bold.

Test Material =	Air	PRINT Placebo	PRINT-Tre		
Treprostinil Dose Level (mg/kg/day) =	0	0	0.17	0.68	1.37
Trehalose Dose Level (mg/kg/day) =	0	281	33	134	267
<i>Males</i>					
Starting weight (Day 1) (g)	301	309	315	312	312
After 4 doses (Day 5) (g)	324	326	337	324	322
Change					
Absolute (g)	+23	+17	+22	+12	+10
Relative to Air Control	---	-6	-1	-11	-13
After 7 doses (fasted Day 8) (g)	300	302	310	301	298
Change					
Absolute (g)*	-1	-7	-5	-10	-14
Relative to Air Control	---	-6	-4	-9	-13
<i>Females</i>					
Starting weight (Day 1) (g)	220	223	220	227	226
After 4 doses (Day 5) (g)	231	235	232	237	231
Change					
Absolute (g)	+11	+12	+12	+10	+5
Relative to Air Control	---	+1	+1	-1	-6
After 7 doses (fasted Day 8) (g)	205	209	204	213	211
Change					
Absolute (g)*	-15	-14	-16	-14	-15
Relative to Air Control	---	+1	-1	-1	0

*All animals were fasted overnight prior to necropsy.

[00386] Remaining differences were considered incidental and of no biological significance.

[00387] Hematology

[00388] The only differences in mean hematology parameters potentially related to administration of the test or control item were greater mean reticulocyte counts in all groups given PRINT-Tre, relative to the air control group. The magnitude of difference was dose-related but statistically significant only in males. The pattern of differences implicates the active ingredient treprostnil, not one of the excipients in PRINT-Tre.

[00389] These data are summarized in the table below, with differences potentially related to treprostnil in bold.

Test Material =	Air	PRINT Placebo	PRINT-Tre		
Treprostnil Dose Level (mg/kg/day) =	0	0	0.17	0.68	1.37
Trehalose Dose Level (mg/kg/day) =	0	281	33	134	267
<i>Reticulocyte count</i>					
Males					
Mean (x 10 ¹² /L)	0.226	0.228	0.309	0.333	0.337
Relative to Air Control	---	+1%	+37%	+47%	+49%
Females					
Mean (x 10 ¹² /L)	0.179	0.176	0.214	0.290	0.283
Relative to Air Control	---	+1%	+20%	+62%	+58%

[00390] An increase in reticulocyte count is an appropriate response to an increased demand for RBCs. In this study, greater reticulocyte counts were not associated with differences in circulating erythron mass (i.e., no differences in RBC count, haemoglobin concentration, or haematocrit). This suggests that the increased release of reticulocytes was accompanied by, and probably a response to, an increased rate of RBC loss, and that the erythropoietic response was adequate to maintain normal circulating RBC numbers.

[00391] Remaining differences among mean hematology parameters were considered incidental and of no biological significance.

[00392] Coagulation

[00393] There were no differences in mean coagulation parameters that were considered to be related to administration of the test or control item. All differences were considered incidental and of no biological significance.

[00394] Clinical Chemistry

[00395] There were no differences in mean clinical chemistry parameters that were considered to be related to administration of the test or control item. All differences were considered incidental and of no biological significance.

[00396] Urinalysis

[00397] There were no differences in the urinalysis parameters that were considered to be related to administration of the test or control item. All differences were considered incidental and of no biological significance.

[00398] Organ Weights

[00399] Differences in mean organ weight potentially related to administration of the test or control item were noted for lungs, adrenal glands, thymus, and testes.

[00400] Remaining differences in mean organ weight were considered incidental and of no biological significance.

[00401] Lungs

[00402] Mean lungs/trachea weights (absolute and relative to body weight) were greater in all groups given the test or control item, compared to the air control group. The differences were greater with PRINT-Tre than with PRINT Placebo, and the differences were dose-related for PRINT-Tre. This pattern suggests that administration of the excipients (likely trehalose) resulted in a slight (15% to 17%) increase in lung weight, which was exacerbated by co-administration of treprostinil as the lung weights of PRINT-Tre groups were increased compared to the lung weights of the PRINT Placebo group.

[00403] There was a histopathologic finding in the lungs that might have accounted for the greater lung weight; specifically, increased alveolar macrophages with basophilic vacuolated cytoplasm in the lungs of all rats given PRINT Placebo or PRINT-Tre at ≥ 0.68 mg/kg/day. However, neither the distribution of this histopathologic finding across groups nor the grade of the finding correlated well with the differences in mean lung weight, suggesting that some other factor was responsible. Because lungs were weighed before fixation, it is possible that some material responsible for the greater weight was removed during tissue fixation and processing.

[00404] Lung weight data are summarized in the table below, with differences potentially related to PRINT Placebo and PRINT-Tre in bold.

Mean Lung Weight Data

Test Material =	Air	PRINT Placebo	PRINT-Tre		
Treprostinal Dose Level (mg/kg/day) =	0	0	0.17	0.68	1.37
Trehalose Dose Level (mg/kg/day) =	0	281	33	134	267
Males					
Absolute weight (g)	1.39	1.60	1.70	1.78*	1.90*
Relative to Air Control	---	+15%	+22%	+28%	+37%
Relative weight (% body weight)	0.46	0.53	0.55	0.59*	0.64*
Relative to Air Control	---	+15%	+20%	+28%	+39%
Females					
Absolute weight (g)	1.09	1.27	1.31*	1.48*	1.44*
Relative to Air Control	---	+17%	+20%	+36%	+32%
Relative weight (% body weight)	0.53	0.61	0.64	0.70*	0.68*
Relative to Air Control	---	+15%	+21%	+32%	+28%

*Statistically significant compared to air control; Dunnett's 2-sided, $p < 0.05$

[00405] Thymus

[00406] Mean thymus weights (absolute and relative to body weight) were slightly lower in both sexes given PRINT-Tre at 0.68 mg/kg/day and in both sexes given to PRINT-Tre at 1.37 mg/kg/day, relative to the air control group (though not statistically significantly different). The pattern of differences implicates the active ingredient treprostinal, not one of the excipients in PRINT-Tre as differences were also seen between PRINT-Tre groups and PRINT Placebo

group. Lower thymus weight was not associated with lower lymphocyte count or with any histopathologic findings.

[00407] Lower thymus weight is one common manifestation of nonspecific physiological or psychological stress (Everds et al., 2013). Because this finding was associated with reduced weight gain (growth) and sometimes also with greater adrenal glands weight, it was most likely secondary to stress and not a direct effect of treprostnil.

[00408] Thymus weight data are summarized in the table below, with differences potentially related to treprostnil in bold.

Mean Thymus Weight Data

Test Material =	Air	PRINT Placebo	PRINT-Tre		
Treprostnil Dose Level (mg/kg/day) =	0	0	0.17	0.68	1.37
Trehalose Dose Level (mg/kg/day) =	0	281	33	134	267
Males					
Absolute weight (mg)	504	593	537	388	429
Relative to Air Control	---	+18%	+7%	-23%	-15%
Relative weight (% body weight)	0.168	0.198	0.173	0.128	0.143
Relative to Air Control	---	+18%	+3%	-24%	-15%
Females					
Absolute weight (mg)	469	437	465	428	352
Relative to Air Control	---	-7%	-1%	-9%	-25%
Relative weight (% body weight)	0.229	0.210	0.228	0.202	0.166
Relative to Air Control	---	-8%	±0%	-12%	-28%

[00409] Adrenal Glands

[00410] Mean adrenal glands weight (absolute and relative to body weight) was greater in males given PRINT-Tre at 0.17 mg/kg/day and in both sexes given to PRINT-Tre at 1.37 mg/kg/day, relative to the air control group (though not statistically significantly different). While the differences may have been due to chance and a consequence of the small group sizes (3/sex), the pattern of differences raises the possibility that they are related to administration of

treprostinil, at least at the high-dose level as differences were also seen between the high dose PRINT-Tre group and the PRINT Placebo group. Greater adrenal glands weight was not associated with any histopathologic findings.

[00411] Greater adrenal glands weight is one common manifestation of nonspecific physiological or psychological stress (Everds et al., 2013). Because this finding was associated with reduced weight gain (growth) and lower thymus weight at the high-dose level, it was most likely secondary to stress and not a direct effect of treprostinil.

[00412] Adrenal glands weight data are summarized in the table below, with differences potentially related to treprostinil in bold.

Mean Adrenal Glands Weight Data

Test Material =	Air	PRINT Placebo	PRINT-Tre		
Treprostinil Dose Level (mg/kg/day) =	0	0	0.17	0.68	1.37
Trehalose Dose Level (mg/kg/day) =	0	281	33	134	267
Males					
Absolute weight (mg)	62	71	76	68	78
Relative to Air Control	---	+15%	+23%	+10%	+26%
Relative weight (% body weight)	0.021	0.023	0.025	0.023	0.027
Relative to Air Control	---	+10%	+19%	+10%	+29%
Females					
Absolute weight (mg)	74	73	70	76	89
Relative to Air Control	---	-1%	-5%	+3%	+20%
Relative weight (% body weight)	0.036	0.035	0.035	0.036	0.042
Relative to Air Control	---	-3%	-3%	±0%	+17%

[00413] Testes

[00414] There was a trend toward slightly lower mean testes weight (absolute and relative to body weight) in groups given PRINT-Tre at ≥ 0.68 mg/kg/day, relative to the air control group. While the differences may have been due to chance and a consequence of the small group sizes (3/sex), the pattern of differences raises the possibility that they are related to administration of

treprostiniil as differences were also seen between the mid and high dose PRINT-Tre groups and the PRINT Placebo group. Slightly lower testes weight was not associated with any histopathologic findings.

[00415] Testes weight data are summarized in the table below, with differences potentially related to treprostiniil in bold.

Mean Testes Weight Data

Test Material =	Air	PRINT Placebo	PRINT-Tre		
Treprostiniil Dose Level (mg/kg/day) =	0	0	0.17	0.68	1.37
Trehalose Dose Level (mg/kg/day) =	0	281	33	134	267
Absolute weight (g)	3.51	3.40	3.39	3.25	3.15
Relative to Air Control	---	-3%	-3%	-7%	-10%
Relative weight (% body weight)	1.17	1.13	1.10	1.08	1.06
Relative to Air Control	---	-3%	-6%	-8%	-9%

[00416] Macroscopic Findings

[00417] There was no evidence of test item-related macroscopic findings at necropsy.

[00418] All findings were considered to be incidental as they were not dose-related, of low incidence, or occurred in the air control, placebo control and treated animals.

[00419] Microscopic Findings

[00420] Treatment-related findings were observed in the lungs, anterior nasal cavity, and nasopharynx. All other microscopic findings were considered to be incidental or procedure-related.

[00421] Lungs

[00422] In the lungs, minimal to mild increased alveolar macrophages with basophilic vacuolated cytoplasm were observed in all rats given PRINT Placebo or PRINT-Tre at ≥ 0.68 mg/kg/day. The pattern of this finding across groups indicates that it is a response to the

excipients (likely trehalose). There were no associated inflammatory changes in the lungs. Increased alveolar macrophages are a common finding in inhalation toxicity studies with powders. It reflects normal pulmonary clearance of inhaled particles and is not considered to be adverse.

[00423] These data are summarized in the table below, with differences potentially related to test or control item in bold.

Incidence and Grade of Increased Alveolar Macrophages

Test Material =	Air	PRINT Placebo	PRINT-Tre		
Treprostinil Dose Level (mg/kg/day) =	0	0	0.17	0.68	1.37
Trehalose Dose Level (mg/kg/day) =	0	281	33	134	267
Males					
Incidence	0/3	3/3	0/3	3/3	3/3
Mean grade	---	1.7	---	1.0	1.7
Females					
Incidence	0/3	3/3	0/3	3/3	3/3
Mean grade	---	2.0	---	1.0	1.7

[00424] Nasal Cavity and Nasopharynx

[00425] Goblet-cell hypertrophy/hyperplasia was seen in the cranial portion of the nasal cavity and in the nasopharynx of at least one rat in all groups given PRINT Placebo or PRINT-Tre, but the incidence was greater in groups given PRINT-Tre at ≥ 0.68 mg/kg/day, and the mean grade was greater in the group given PRINT-Tre at 1.37 mg/kg/day. This pattern suggests that administration of the excipients (likely trehalose) resulted in occasional goblet-cell changes, which were exacerbated by co-administration of treprostinil at higher dose levels.

[00426] Goblet cell hypertrophy/hyperplasia in the anterior nasal cavity and nasopharynx is one of the most frequently observed lesions in rodents exposed to irritant compounds. This finding generally is considered a nonspecific protective or adaptive response and not adverse.

[00427] These data are summarized in the table below, with differences potentially related to test or control item in bold.

Incidence and Grade of Goblet-cell Hypertrophy/Hyperplasia

Test Material =	Air	PRINT Placebo	PRINT-Tre		
Treprostinil Dose Level (mg/kg/day) =	0	0	0.17	0.68	1.37
Trehalose Dose Level (mg/kg/day) =	0	281	33	134	267
<i>Nasal Cavity</i>					
Males					
Incidence	0/3	1/3	1/3	3/3	3/3
Mean grade	---	1.0	1.0	1.0	1.3
Females					
Incidence	0/3	0/3	0/3	1/3	2/3
Mean grade	---	---	---	1.0	1.5
<i>Nasopharynx</i>					
Males					
Incidence (all graded minimal)	0/3	0/3	0/3	3/3	3/3
Females					
Incidence(all graded minimal)	0/3	1/3	0/3	3/3	3/3

[00428] Discussion and Conclusions

[00429] Rats tolerated daily administration of PRINT Placebo or PRINT-Tre at up to 1.37 mg/kg/day by 4-hour inhalation for 7 days.

[00430] The only findings potentially related to administration of excipients (likely trehalose) were:

- Increased alveolar macrophages with basophilic vacuolated cytoplasm in all rats given PRINT Placebo or PRINT-Tre at ≥ 0.68 mg/kg/day; *i.e.*, in rats given trehalose at ≥ 134 mg/kg/day. The mean grade of this finding increased with trehalose dose level. This finding was not associated with inflammatory changes in the lungs and was considered to reflect normal pulmonary clearance of inhaled particles. It was not considered to be adverse.
- Greater mean lung weight in groups given PRINT Placebo or PRINT-Tre. The weight differences were unrelated to trehalose dose level. Instead, they were greater with PRINT-Tre than with PRINT Placebo and were dose-related for PRINT-Tre. This pattern suggests that administration of the excipients (likely trehalose) resulted in a slight (15% to 17%) increase in lung weight, which was exacerbated by co-administration of treprostinil. Of note, the pattern of differences in lung weight across groups is distinct from the pattern of increased alveolar macrophages across groups, indicating that the weight differences were not a consequence of increased macrophages. There were no histopathologic findings in the lungs that might have accounted for the greater lung weight. Because lungs were weighed before fixation, it is possible that some material responsible for the greater weight was removed during tissue fixation and processing.
- Minimal goblet-cell hypertrophy/hyperplasia in the cranial portion of the nasal cavity of at least one rat in all groups given PRINT Placebo or PRINT-Tre. The incidence of this finding was unrelated to trehalose dose level. Instead, the incidence was greater with PRINT-Tre at ≥ 0.68 mg/kg/day, and the mean grade was greater with PRINT-Tre at 1.37 mg/kg/day. This pattern suggests that administration of the excipients (likely trehalose) resulted in occasional goblet-cell changes, which were exacerbated by co-administration of treprostinil at higher dose levels. Goblet-cell hypertrophy/hyperplasia was considered a nonspecific protective or adaptive response and not adverse.

[00431] Besides exacerbating lung weight differences and goblet-cell hypertrophy/hyperplasia in the nasal cavity and nasopharynx, the following other findings were potentially related to administration of treprostinil as PRINT-Tre:

- Slightly less growth (weight gain) in males at 0.68 mg/kg/day and in both sexes at 1.37 mg/kg/day.

- Greater mean reticulocyte counts at all dose levels, with the magnitude of difference increasing with dose level. This was not considered adverse in and of itself; however, it likely reflected an appropriate adaptive response to an increased rate of RBC loss or turnover.
- Greater mean adrenal glands weight in males at 0.17 mg/kg/day, lower mean thymus weight in both sexes at 0.68 mg/kg/day, and greater mean adrenal glands weight and lower mean thymus weight in both sexes at 1.37 mg/kg/day. There were no associated differences in lymphocyte count or histopathologic findings in either organ. These organ weight differences most likely reflected stress and were not a direct effect of treprostinil.

[00432] Based on these results, it is recommended that an upcoming 14-day GLP inhalation toxicology study in rats target similar dose levels as used in the current study.

[00433] CLINICAL STUDY: LIQ861

[00434] Randomized, Placebo-controlled, Single-ascending Dose Study Evaluating Pharmacokinetics (PK) and Safety in Healthy Male and Female Volunteers

[00435] A clinical study was conducted to (1) determine the single-dose safety and tolerability and (2) evaluate the single-dose pharmacokinetics of particles of the invention upon administration to healthy male and female subjects.

[00436] Six cohorts were evaluated: dose levels of 25, 50, 75, 100, 125 and 150 µg of treprostinil respectively. In each cohort, eight subjects were randomly assigned in a 3:1 blinded ratio and received a single dose of either particles of the invention (N = 6) or placebo particles (N = 2).

[00437] Blood was collected for PK evaluation at T = 0, 5, 10, 15, 20, 25, 30, 45, 60, 90, and 120 minutes and 3, 4, 6, and 8 hours post-dose.

[00438] Cohort 1

[00439] Eight subjects were enrolled and dosed in Cohort 1. Six subjects received active treatment and 2 received placebo. Active treatment was administered by dry powder inhalation (DPI) as a single capsule of 25 µg treprostinil strength, and placebo treatments were administered

by DPI as a single capsule of the placebo formulation. All inhalations were administered using the RS00 inhaler.

[00440] Blood samples were obtained prior to dosing and at nominal times of 0.083, 0.167, 0.25, 0.33, 0.417, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, and 8 hours after inhalation. Analysis of plasma concentration versus time data for calculation of standard pharmacokinetic (PK) parameters following inhalation was conducted using Phoenix WinNonlin version 6.3 using scheduled blood sampling times. Plasma concentrations were provided only for subjects on active dose and random subject numbers were assigned by the bioanalytical laboratory to retain the study blind.

[00441] The table shown in Figure 3A contains a summary of the treprostinil concentration-time data for individual subjects with descriptive statistics for the six active subjects in Cohort 1. Preliminary non-compartmental PK parameters for treprostinil are summarized in the table shown in Figure 3B. The highest concentrations for three of the six subjects occurred at 0.33 hours post-inhalation; one subject each had a T_{max} of 0.167, 0.25, and 0.417 hours post-dose. Concentrations subsequently decayed with a single-phase disposition profile, as shown in the log-linear plots. At two hours after inhalation, two of six active subjects had measurable concentrations of treprostinil and only one subject had measurable concentrations at 2.5 and 3 hours after inhalation. No subjects had quantifiable concentrations after the 3 hour timepoint.

[00442] The C_{max} averaged 0.364 ng/mL and the most frequent T_{max} was 0.33 hours after inhalation. AUC_{inf} values averaged 0.301 h*ng/mL with a CV% of 30.2%. The apparent volume of distribution (V_z/F) averaged 68.1 L. Oral clearance (CL/F) averaged 91.0 L/h and ranged from 59.1 to 150. Variability in the CL/F value had a CV% of 35.8%.

[00443] Cohort 2

[00444] Nine subjects were enrolled and dosed in Cohort 2. At least six subjects received active treatment and at least 2 received placebo; 1 subject withdrew before the 2 hour PK sample and was replaced. Subjects with truncated sampling schedules have been excluded in this interim analysis. Active treatment was administered by dry powder inhalation (DPI) as a single capsule of 50 µg treprostinil strength, and placebo treatments were administered by DPI as a

single capsule of the placebo formulation. All inhalations were administered using the RS00 inhaler.

[00445] Blood samples were obtained prior to dosing and at nominal times of 0.083, 0.167, 0.25, 0.33, 0.417, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, and 8 hours after inhalation. Analysis of plasma concentration versus time data for calculation of standard pharmacokinetic (PK) parameters following inhalation was conducted using Phoenix WinNonlin version 6.3 using scheduled blood sampling times. Plasma concentrations were provided only for subjects on active dose and random subject numbers were assigned by the bioanalytical laboratory to retain the study blind.

[00446] The table shown in Figure 4A contains a summary of the treprostinil concentration-time data for individual subjects with descriptive statistics for the six active subjects in Cohort 2.

[00447] The highest concentrations for four of the six subjects occurred at 0.17 hours post-inhalation; of the remaining subjects, one had T_{max} at 0.083 hours post-dose and one at 0.417 hours post-dose. At 2.5 hours after inhalation, 2 of 6 active subjects had measurable concentrations of treprostinil and only one subject had measurable concentrations at 3 hours after inhalation. No subjects had quantifiable concentrations after the 3 hour timepoint.

[00448] Preliminary non-compartmental PK parameters for treprostinil for Cohort 2 are summarized in the table shown in Figure 4B. The C_{max} averaged 0.572 ng/mL and the most frequent T_{max} was 0.167 hours after inhalation. AUC_{inf} values averaged 0.422 h*ng/mL with a CV% of 62.8%. The apparent volume of distribution (V_z/F) averaged 110 L. Oral clearance (CL/F) averaged 208 L/h and ranged from 67 to 624. Variability in the CL/F value had a CV% of 101.5%.

[00449] By comparison, the C_{max} for Cohort 1 averaged 0.364 ng/mL and the AUC_{inf} values averaged 0.301 h*ng/mL. Thus, a doubling of the treprostinil dose resulted in an approximate 50% increase in exposure. The V_z/F and the CL/F values were considerably higher for Cohort 2 and with greater variability.

[00450] Cohort 3

[00451] Eight subjects were enrolled and dosed in Cohort 3. Six subjects received active treatment and two received placebo. Active treatment was administered by dry powder inhalation (DPI) as a single capsule of 75 µg treprostinil strength and placebo treatments were administered by DPI as a single capsule of the placebo formulation. All inhalations were administered using the RS00 inhaler.

[00452] Blood samples were obtained prior to dosing and at nominal times of 0.083, 0.167, 0.25, 0.33, 0.417, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, and 8 hours after inhalation. Analysis of plasma concentration versus time data for calculation of standard pharmacokinetic (PK) parameters following inhalation was conducted using Phoenix WinNonlin version 6.3 using scheduled blood sampling times. Plasma concentrations were provided only for subjects on active dose and random subject numbers were assigned by the bioanalytical laboratory to retain the study blind.

[00453] The table shown in Figure 5A contains a summary of the treprostinil concentration-time data for individual subjects with descriptive statistics for the 6 active subjects in Cohort 3.

[00454] The highest concentrations for three of the six subjects occurred at 0.25 hours post-inhalation; of the remaining subjects, 1 had Tmax at 0.083 hours post-dose, 1 at 0.17 hours post-dose, and 1 at 0.417 hours post-dose. At 3 hours after inhalation, two of six active subjects had measurable concentrations of treprostinil. No subjects had quantifiable concentrations after the 3 hour timepoint.

[00455] Preliminary non-compartmental PK parameters for treprostinil for Cohort 3 are summarized in the table shown in Figure 5B. The Cmax averaged 0.728 ng/mL and the most frequent Tmax was 0.25 hours after inhalation. AUCinf values averaged 0.757 h*ng/mL with a CV% of 39.4%. The apparent volume of distribution (Vz/F) averaged 97 L. Oral clearance (CL/F) averaged 112 L/h and ranged from 58 to 161. Variability in the CL/F value had a CV% of 39.4%.

[00456] By comparison, the Cmax for Cohort 1 and Cohort 2 averaged 0.364 ng/mL and 572 ng/mL, respectively, while the AUCinf values averaged 0.301 h*ng/mL and 0.422 h*ng/mL. Thus, a tripling of the dose from Cohort 1 resulted in an approximate 100 – 150% increase in

exposure. The CL/F values for Cohort 3 were more consistent with Cohort 1, and with similar variability, than what was observed in Cohort 2. The results indicate that both C_{max} and AUC_{inf} may be increasing proportionately to the increase in the dose and that the CL is independent of dose over the range of 25 to 75 µg treprostinil.

[00457] Cohort 4

[00458] Eight subjects were enrolled and dosed in Cohort 4. Six subjects received active treatment and two received placebo. Active treatment of 100 µg treprostinil was administered by dry powder inhalation (DPI) as 2 capsules of 50 µg treprostinil strength and placebo treatments were administered by DPI as 2 capsules of the placebo formulation. All inhalations were administered using the RS00 inhaler.

[00459] Blood samples were obtained prior to dosing and at nominal times of 0.083, 0.167, 0.25, 0.33, 0.417, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, and 8 hours after inhalation. Analysis of plasma concentration versus time data for calculation of standard pharmacokinetic (PK) parameters following inhalation was conducted using Phoenix WinNonlin version 6.3 using scheduled blood sampling times. Plasma concentrations were provided only for subjects on active dose and random subject numbers were assigned by the bioanalytical laboratory to retain the study blind.

[00460] The table shown in Figure 6A contains a summary of the treprostinil concentration-time data for individual subjects with descriptive statistics for the six active subjects in Cohort 4. The highest concentrations for 2 of the 6 subjects occurred at 0.25 hours post-inhalation; of the remaining subjects, 2 had T_{max} at 0.5 hours post-dose, 1 at 0.17 hours post-dose, and 1 at 0.33 hours post-dose. At 4 hours after inhalation, 3 of 6 active subjects had measurable concentrations of treprostinil. No subjects had quantifiable concentrations at the 6 or 8 hour timepoints.

[00461] Preliminary non-compartmental PK parameters for treprostinil for Cohort 4 are summarized in Figure 6B. The C_{max} averaged 1.08 ng/mL and the most frequent T_{max} values were observed at 0.25 hours and 0.5 hours after inhalation. AUC_{inf} values averaged 1.22 h*ng/mL with a CV% of 18.4%. The apparent volume of distribution (V_z/F) averaged 96 L.

Oral clearance (CL/F) averaged 84.8 L/h and ranged from 68.3 to 122. Variability (CV%) in the CL/F value was 22.8%.

[00462] By comparison, the C_{max} for Cohorts 1, 2, and 3 averaged 0.364 ng/mL, 0.572 ng/mL, and 0.728 ng/mL respectively, while the AUC_{inf} values averaged 0.301 h*ng/mL, 0.422 h*ng/mL, and 0.757 h*ng/mL. Thus, a quadrupling of the dose from Cohort 1 resulted in an approximate 200 – 300% increase in exposure, while a doubling of the dose from Cohort 2 resulted in an approximate 2-fold increase in exposure. The results indicate that both C_{max} and AUC_{inf} may be increasing proportionately to the increase in the dose and that the CL/F is independent of dose over the range of 25 to 100 µg treprostinil.

[00463] Cohort 5

[00464] Eight subjects were enrolled and dosed in Cohort 5. Six subjects received active treatment and two received placebo. Active treatment of 125 µg treprostinil was administered by dry powder inhalation (DPI) as 1 capsule of 75 µg and 1 capsule of 50 µg treprostinil strength and placebo treatments were administered by DPI as 2 capsules of the placebo formulation. All inhalations were administered using the RS00 inhaler.

[00465] Blood samples were obtained prior to dosing and at nominal times of 0.083, 0.167, 0.25, 0.33, 0.417, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, and 8 hours after inhalation. Analysis of plasma concentration versus time data for calculation of standard pharmacokinetic (PK) parameters following inhalation was conducted using Phoenix WinNonlin version 6.3 using scheduled blood sampling times. Plasma concentrations were provided only for subjects on active dose and random subject numbers were assigned by the bioanalytical laboratory to retain the study blind.

[00466] The table shown in Figure 7A contains a summary of the treprostinil concentration-time data for individual subjects with descriptive statistics for the 6 active subjects in Cohort 5. The highest concentrations for 3 of the 6 subjects occurred at 0.17 hours post-inhalation; of the remaining subjects, 2 had T_{max} at 0.33 hours post-dose, and 1 at 0.42 hours post-dose. At 3.5 and 4 hours after inhalation, only 1 of 6 active subjects had measurable concentrations of treprostinil. No subjects had quantifiable concentrations at the 6 or 8 hour timepoints.

[00467] Preliminary non-compartmental PK parameters for treprostinil for Cohort 5 are summarized in Figure 7B. The C_{max} averaged 1.19 ng/mL and the most frequent T_{max} values were observed at 0.17 hours after inhalation. AUC_{inf} values averaged 1.15 h*ng/mL with a CV% of 44.9%. The apparent volume of distribution (V_z/F) averaged 101 L. Oral clearance (CL/F) averaged 141 L/h and ranged from 65.7 to 336. Variability (CV%) in the CL/F value was 69.9%.

[00468] By comparison, the C_{max} for Cohorts 1, 2, 3, and 4 averaged 0.364 ng/mL, 0.572 ng/mL, 0.728 ng/mL, and 1.08 ng/mL respectively, while the AUC_{inf} values averaged 0.301 h*ng/mL, 0.422 h*ng/mL, 0.757 h*ng/mL, and 1.22 h*ng/mL. Thus, a quintupling of the dose from Cohort 1 resulted in an approximate 220 – 280% increase in exposure. The results indicate that both C_{max} and AUC_{inf} may be increasing proportionately to the increase in the dose and that the CL/F is independent of dose over the range of 25 to 125 µg treprostinil.

[00469] Cohort 6

[00470] Cohort 6 was conducted as an original and a repeat. In each Cohort 6 (original and repeat), eight subjects were enrolled and dosed. Six subjects received active treatment and two received placebo. Active treatment of 150 µg treprostinil was administered by dry powder inhalation (DPI) as 2 capsules of 75 µg treprostinil strength and placebo treatments were administered by DPI as 2 capsules of the placebo formulation. All inhalations were administered using the RS00 inhaler. Cohort 6 original included some mechanical device failures and subject non-compliance with instructions, giving rise to Cohort 6 repeat.

[00471] Blood samples were obtained prior to dosing and at nominal times of 0.083, 0.167, 0.25, 0.33, 0.417, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, and 8 hours after inhalation. Analysis of plasma concentration versus time data for calculation of standard pharmacokinetic (PK) parameters following inhalation was conducted using Phoenix WinNonlin version 6.3 using scheduled blood sampling times. Plasma concentrations were provided only for subjects on active dose and random subject numbers were assigned by the bioanalytical laboratory to retain the study blind.

[00472] The table shown in Figure 8A contains a summary of the treprostinil concentration-time data for individual subjects with descriptive statistics for the six active subjects in Cohort 6-R. The highest concentrations for 2 of the 6 subjects occurred at 0.25 hours post-inhalation and at 0.33 hours post-inhalation. In the remaining 2 subjects, T_{max} occurred at the 0.167 and 0.417 hours post-dose timepoints. At 4 hours after inhalation, 4 of 6 active subjects had measurable concentrations of treprostinil. No subjects had quantifiable concentrations at the 6 or 8 hour timepoints.

[00473] Preliminary non-compartmental PK parameters for treprostinil for Cohort 6-R are summarized in Figure 8B. Preliminary non-compartmental PK parameters for treprostinil for Cohort 6-Original are summarized in Figure 8C. Mean concentration-time data for each of the six cohorts is displayed on a linear scale in Figure 8D. The C_{max} averaged 1.45 ng/mL and the most frequent T_{max} values were observed at 0.25 and 0.33 hours after inhalation. AUC_{inf} values averaged 1.62 h*ng/mL with a CV% of 68.3%. The apparent volume of distribution (V_z/F) averaged 107 L. Oral clearance (CL/F) averaged 126 L/h and ranged from 51.8 to 245. Variability (CV%) in the CL/F value was 68.3%.

[00474] By comparison, the C_{max} for Cohorts 1, 2, 3, 4, 5, and the combined Cohort 6 averaged 0.364 ng/mL, 0.572 ng/mL, 0.728 ng/mL, 1.08 ng/mL, 1.19 ng/mL, and 1.21 ng/mL, respectively (Figure 8E), while the AUC_{inf} values averaged 0.301 h*ng/mL, 0.422 h*ng/mL, 0.757 h*ng/mL, 1.22 h*ng/mL, 1.15 h*ng/mL, and 1.37 h*ng/mL (Figure 8F). Thus, a 6-fold increase of the dose from Cohort 1 to the combined Cohort 6 observations resulted in an approximate 260 – 400% increase in exposure, while tripling from Cohort 2 and doubling from Cohort 3 resulted in approximate increases of exposure by 130 – 255% and 81 – 98%, respectively. Moreover, plots of the relationship between dose and C_{max} and AUC_{inf} are displayed in Figure 8E and Figure 8F, respectively. The results indicate that both C_{max} and AUC_{inf} may be increasing proportionately to the increase in the dose. It was observed at the CRU during the original 150 µg dosing, however, that there were several apparent device failures that may have resulted in incomplete and/or inefficient exposures. It should be noted that no device failures were noted during the repeat dosing and, while mean values may be higher than in the initial cohort, the variability in the repeated cohort is greater. A plot of the relationship between dose and CL/F (Figure 8G) shows that the CL/F is independent of dose over the range

of 25 to 150 µg treprostinil, which suggests that PK of treprostinil has a proportional relationship to dose over the range of 25 to 150 µg treprostinil.

[00475] CLINICAL CONCLUSIONS

[00476] LIQ861 was dosed at levels of 25, 50, 75, 100, 125 and 150 µg treprostinil from either a single capsule (25, 50 and 75 mcg doses) or a combination of two lower capsular strengths (for 100, 125 and 150 mcg doses), each capsule either undergoing either a single breath or two breaths. According to embodiments of the present invention, novel capsule to particle powder to active ingredient ratios, and breath per capsule and powder per breath ratios for human dosing are included in the following table.

Patient presentation of particle powder and active agent per capsule per breath for particle formulation having 0.5 percent active agent load						
Capsules	1	1	1	2	2	2
Particle Powder in mg	5	10	15	Combination of two 50 mcg capsules or one 25 mcg and one 75 mcg	Combination of, ex., 1 at 50 mcg and 1 at 75 mcg	Combination of, ex., two capsules at 75 mcg
Active Agent Load in mcg	25	50	75	Varies, see above	Varies, see above	Varies, see above
Breaths to Deliver	1 to 2	1 to 2	1 to 2	1 to 2 per capsule	1 to 2 per capsule	1 to 2 per capsule

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Particle Powder per Breath in mg	2.5-5	5-10	7.5-15	Varies, up to 15	Varies, up to 15	Varies, up to 15
Active Agent per Breath in mcg	12.5-25	25-50	37.5-75	Varies, up to 75	Varies, up to 75	Varies, up to 75

[00477] According to such embodiments, as shown in the above table, each breath can receive from 2.5 – 15 mg of particle power and from 12.5 – 75 mcg of active agent.

[00478] For the given treprostinil delivered in the given mass of particle powder loaded into a capsule and delivered through a dry powder inhaler results in the human clinical outcomes are included in the following table for LIQ861.

LIQ861 Clinical Outcomes	C_{max} (ng/mL)	T_{max}^a (h)	t_{1/2} (h)	AUC_{last} (h*ng/mL)	AUC_{inf} (h*ng/mL)	CL/F (L/h)	Vz/F (L)
25 mcg Treprostinil	0.36 (0.12)	0.33 (0.17, 0.42)	0.52 (0.16)	0.27 (0.09)	0.3 (0.09)	91 (32.6)	68.1 (27.4)
50 mcg Treprostinil	0.57 (0.37)	0.17 (0.08, 0.42)	0.45 (0.12)	0.4 (0.26)	0.42 (0.27)	208 (211)	110 (66.6)
75 mcg Treprostinil	0.73 (0.3)	0.25 (0.08, 0.42)	0.62 (0.18)	0.72 (0.31)	0.76 (0.31)	112 (38.5)	97 (29.1)
100 mcg Treprostinil	1.08 (0.31)	0.29 (0.17, 0.5)	0.78 (0.13)	1.18 (0.22)	1.22 (0.23)	84.8 (19.3)	95.5 (28.2)
125 mcg Treprostinil	1.19 (0.53)	0.25 (0.17, 0.42)	0.53 (0.07)	1.12 (0.51)	1.15 (0.52)	141 (98.8)	101 (58.7)
150 mcg Treprostinil	1.21 (0.3)	0.29 (0.08, 0.42)	0.66 (0.15)	1.33 (0.44)	1.37 (0.42)	119 (35.8)	115 (51.4)
150 mcg Treprostinil	1.45 (0.63)	0.29 (0.17, 0.42)	0.64 (0.11)	1.58 (0.85)	1.62 (0.87)	126 (80.3)	107 (54)

Abbreviations: SD = standard deviation; C_{max} = maximum observed plasma concentration; T_{max} = time to C_{max};

t_{1/2} = half-life; AUC = area under the curve; CL/F = apparent clearance; Vz/F = apparent volume of distribution

All values except for T_{max} are reported as arithmetic means with SD in parentheses.

^a T_{max} reports median values with minimum and maximum values in parentheses

[00479] For comparison, TYVASO (United Therapeutics, Inc.) provides the current standard of treatment for inhaled treprostinil. Such treprostinil is delivered through a nebulizer for the treatment of PAH and is limited to deliver 6mcg of treprostinil per breath, utilizing 9 breaths to reach a 54 mcg dose. The current standard of inhaled treatment has shown to be dose limited to a maximum tolerated dose of 84 mcg of treprostinil, which required 14 breaths to reach such dose. See, Channick, R. et al., Inhaled Treprostinil: a therapeutic review, Drug Design, Development and Therapy 2012:6 19-28; and Nelsen AC, et al., Pharmacokinetics Of Inhaled Treprostinil Sodium In Healthy Volunteers. Am J Respir Crit Care Med. 2010; 181:A3348; both of which are incorporated herein by reference in their entirety.

[00480] In alternative embodiments, particles of the present invention may include 1% treprostinil load, as compared to 0.5% treprostinil load of the LIQ861 particles. According to an

embodiment of the present invention, a plurality of 1% treprostinil particles were fabricated from a solution comprising, weight percent solids in water, of: 1.06% treprostinil sodium, 92.44% trehalose dihydrate, 2% polysorbate 80, 4% L leucine, 0.27% sodium citrate dihydrate, and 0.23% sodium chloride.

[00481] According to a 1 percent treprostinil particle formulation of the present invention, particle powder mass and active agent presented to a patient comprise the following novel capsule to particle powder to active ingredient ratios, and breath per capsule and powder per breath ratios for human dosing.

Patient presentation of particle powder and active agent per capsule per breath for particle formulation having 1 percent active agent load						
Capsules	1	1	1	1	1	1
Particle Powder in mg	2.5	5	7.5	10	12.5	15
Active Agent Load in mcg	25	50	75	100	125	150
Breaths to Deliver	1 to 2	1 to 2	1 to 2	1 to 2	1 to 2	1 to 2
Particle Powder per Breath in mg	1.25-2.5	2.5-5	3.75-7.5	5-10	6.25-12.5	7.5-15
Active Agent per Breath in mcg	12.5-25	25-50	37.5-75	50-100	62.5-125	75-150

[00482] According to such embodiments, as shown in the above table, each breath can receive from 1.25 – 15 mg of particle power and from 12.5 – 150 mcg of active agent.

[00483] For the powder mass found acceptable in LIQ861 initial clinical trial associated with delivery of the 150 mcg dose, at a 1% active drug particle a dose of 300 mcg of active drug can be administered in a safe and acceptable powder mass and excipient quantity.

[00484] Kits

[00485] According to embodiments of the present invention the dry powder inhaler device can be combined into a kit with capsules for use therein. The capsules can be packaged in blister packs with or without desiccant to ensure controlled environment for the LIQ861 particle powder while the traveling with a user. The blister packs can include capsules for a single dosing or multiple capsules for a day, week or month of doses. Typically a patient will treat 4 times per day for the PAH indication. The kit can include capsules comprising dosage strengths of 25, 50, 75, 100, 125, 150, 200, 250, 300 mcg or beyond for the treatment of PAH. The particles of the powder in the capsules of the kits can be particles comprising 0.5% treprostinil or 1% treprostinil.

[00486] Abbreviations and Nomenclature Cross-references

6MWD	6 Minute Walk Distance
AE	Adverse Event
AUC	Area Under the Curve
AUCinf	Area Under the Concentration-Time Curve Extrapolated to Time Infinity
AUClast	Area Under the Concentration-Time Curve to the Last Measured Timepoint
AUCext	Percentage of Area Under the Curve Extrapolated Beyond Last Measureable Concentration
AVT	Acute Pulmonary Vasodilator Testing
BA	Bioavailability
BDI	Borg Dyspnea Index
BLQ	Below the Limit of Quantitation
BMP2	Bone Morphogenic Protein Receptor Type II Gene
BP	British Pharmacopoeia

BTO	Benzidine Triol
CAS	Chemical Abstracts Service
CFR	Code of Federal Regulations
CFU	Colony Forming Unit
cGMP	Current Good Manufacturing Practice
CI	Cardiac Index
CL	Clearance
C _{max}	Maximum Concentration
CMC	Chemistry Manufacturing and Controls
CO	Cardiac Output
COPD	Chronic Obstructive Pulmonary Disease
C _{ss}	Concentration at Steady State
CTEPH	Chronic Thromboembolic Pulmonary Hypertension
CYP	Cytochrome P450
DMF	Drug Master File
DP	Drug Product
DPI	Dry Powder Inhaler
DPPA	Diphenylphosphinic Acid
DRF	Dose Range Finding
DS	Drug Substance
DUSA	Dosage Unit Sampling Apparatus
eCMH	Extended Cochran-Mantel-Haenszel Test
ECG	Electrocardiogram
ED	Emitted Dose
E _{max}	Maximum Effect
EP	European Pharmacopoeia
ERA	Endothelin Receptor Agonists
ET3	Polyethylene Terephthalate Cyclic Trimer
EU	Endotoxin Unit
ESRD	End-Stage Renal Disease
F	Bioavailability
FCR	Fluorocur [®]
FDA	Food and Drug Administration

FPF	Fine Particle Fraction
Frel	Relative Bioavailability
FT-IR	Fourier Transform Infrared Spectroscopy
GC	Gas Chromatography
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GSD	Geometric Standard Deviation
HIAC	High Accuracy Particle Counter
HIV	Human Immunodeficiency Virus
H-L	Hodges-Lehmann
HPLC	High Performance Liquid Chromatography
HPMC	Hydroxypropyl Methylcellulose
HR	Heart Rate
ICH	International Conference on Harmonisation
IM	Intramuscular
IND	Investigational New Drug
INR	International Normalized Ratio
IR	Infrared
ISO	International Organization for Standardization
IV	Intravenous
JP	Japanese Pharmacopoeia
KF	Karl Fischer Titration
LC	Liquid Chromatography
LC-MS	Liquid Chromatography with Mass Spectrometry
LV	Left Ventricular
LVdP/dt	Left Ventricular Contractility
mcg	Micrograms, µg or ug
MDI	Metered Dose Inhaler
MeOH	Methanol
MLWHF	Minnesota Living With Heart Failure Questionnaire
MMAD	Mass Median Aerodynamic Diameter
MTD	Maximum Tolerated Dose
PAPm	Mean Pulmonary Arterial Pressure

NDA	New Drug Application
NF	National Formulary
NGI	Next Generation Impactor™
NMR	Nuclear Magnetic Resonance
NMT	Not More Than
NO	Nitric Oxide
NOAEL	No Observed Adverse Effect Level
NRF	Normal Renal Function
NT	Not Tested
NT-proBNP	N-Terminal of the Prohormone Brain Natriuretic Peptide
NYHA	New York Heart Association
OHSAS	Occupational Health and Safety Advisory Services
OPP	Oriented Polypropylene
PAH	Pulmonary Arterial Hypertension
PAP	Pulmonary Arterial Pressure
PCW	Pulmonary Capillary Wedge pressure
PD	Pharmacodynamics
PDE5	Phosphodiesterase Type 5 Inhibitors
PE	Polyethylene
PET	Polyethylene Terephthalate
PGI ₂	Prostaglandin I ₂ (Prostacyclin)
PH	Pulmonary Hypertension
PK	Pharmacokinetics
PPM	Parts Per Million
PRINT	Particle Replication In Nonwetting Templates
PTFE	Polytetrafluoroethylene
PVR	Pulmonary Vascular Resistance
QID	Quarter in Die (Four Times Daily)
(Q)SAR	Quantitative Structure-Activity Relationship
QTc	Corrected QT Interval
RH	Relative Humidity
RLD	Reference Listed Drug
SAC	Single Actuation Content

SAE	Serious Adverse Event
SAP	Systemic Arterial Pressure
SC	Subcutaneous
SEM	Standard Error of the Mean
SOP	Standard Operating Procedure
SVR	Systemic Vascular Resistance
t _{1/2}	Half-life
TBD	To Be Determined
TK	Toxicokinetics
Tmax	Time of Maximal Concentration
TMB acid	Trimethylbenzoic Acid
TMB-Ald	Trimethylbenzaldehyde
TMP	Trimethylbenzoyl Diphenylphosphine Oxide
TRIUMPH	Treprostinil Sodium Inhalation Used in the Management of Pulmonary Arterial Hypertension (clinical trial)
TTC	Threshold for Toxicological Concern
IUPAC	International Union of Pure and Applied Chemistry
µg or ug	Micrograms or mcg
US	United States
USP	United States Pharmacopeia
WHO	World Health Organization
WRS	Wilcoxon Rank Sum Test
WT	Weight
XRD	X-ray Diffractometer

Product Nomenclature and Reference Table

Term	Designation	Exemplary Embodiment
Drug Substance	DS or treprostinil	Treprostinil, supplied as treprostinil sodium for manufacture of the LIQ861 drug product-intermediate
Drug Product-Intermediate	DP-intermediate or LIQ861 DP-intermediate	Dry powder particles of precise size and shape containing an integrated matrix of treprostinil and excipients that is produced using Liquidia's PRINT® Technology manufacturing process (bulk dry powder prior to capsule filling)
Placebo Drug Product-Intermediate	Placebo DP-intermediate	Identical formulation as the DP-Intermediate, but treprostinil is replaced with an equal mass of trehalose
Inhalation Powder Drug Product	DP or LIQ861 Drug Product or LIQ861	LIQ861 DP-intermediate filled into Size 3 HPMC capsules for oral inhalation, but prior to integration with Inhalation Device
Placebo Drug Product	Placebo	Placebo DP-intermediate filled into Size 3 hydroxypropyl methylcellulose (HPMC) capsules, but prior to integration with the Inhalation Device
Drug Product Strength or Dose	Treprostinil in LIQ861	Amount of treprostinil in drug product
Packaged Drug Product	None	Drug Product in the Primary Packaging
Inhalation Device	Device	Device that is used to deliver the Drug Product

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Premetered Dry Powder Inhaler	DPI	Drug Product integrated with the Inhalation Device; i.e., the final product for patient use
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We claim:

1. A dry powder inhalation treatment for pulmonary arterial hypertension, comprising:
a dose of dry particles comprising greater than 25 micrograms of treprostinil enclosed in a capsule.
2. The dry powder inhalation treatment of claim 1, wherein the dose of dry particles comprises greater than or equal to 100 micrograms of treprostinil.
3. The dry powder inhalation treatment of claim 1, wherein the dose of dry particles comprises greater than or equal to 150 micrograms of treprostinil.
4. The dry powder inhalation treatment of claim 1, wherein the dose of dry particles comprises greater than or equal to 5 mg of the dry particles.
5. The dry powder inhalation treatment of claim 2, wherein the dose of dry particles comprises greater than or equal to 10 mg of the dry particles.
6. The dry powder inhalation treatment of claim 3, wherein the dose of dry particles comprises greater than or equal to 15 mg of the dry particles.
7. A dry powder treatment for pulmonary arterial hypertension, comprising:
a single capsule enclosing 5 mg or more dry particles comprising 25 micrograms of treprostinil per each 5 mg of the dry particles.
8. A method of treating a patient having pulmonary arterial hypertension, comprising:
providing a patient a dry powder inhaler;
providing the patient at least one capsule for use in the dry powder inhaler, wherein the capsule comprises at least 25 micrograms of treprostinil; and
instructing the patient to utilize the dry powder inhaler to inhale the treprostinil.
9. The method of claim 8, wherein the capsule comprises at least 50 micrograms of treprostinil.
10. The method of claim 8, wherein the capsule comprises at least 100 micrograms of treprostinil.
11. The method of claim 8, wherein the capsule comprises at least 150 micrograms of treprostinil.
12. A method of treating a patient having pulmonary arterial hypertension, comprising:
dosing the patient having pulmonary arterial hypertension with a dry powder dose of treprostinil, wherein the dose of treprostinil is greater than 85 micrograms.
13. A dry powder inhalation composition for treating pulmonary arterial hypertension, comprising:

a plurality of dry powder particles comprising treprostinil, a non-reducing sugar, a wetting agent, a hydrophobicity modifying agent, a pH modifying agent and a buffer.

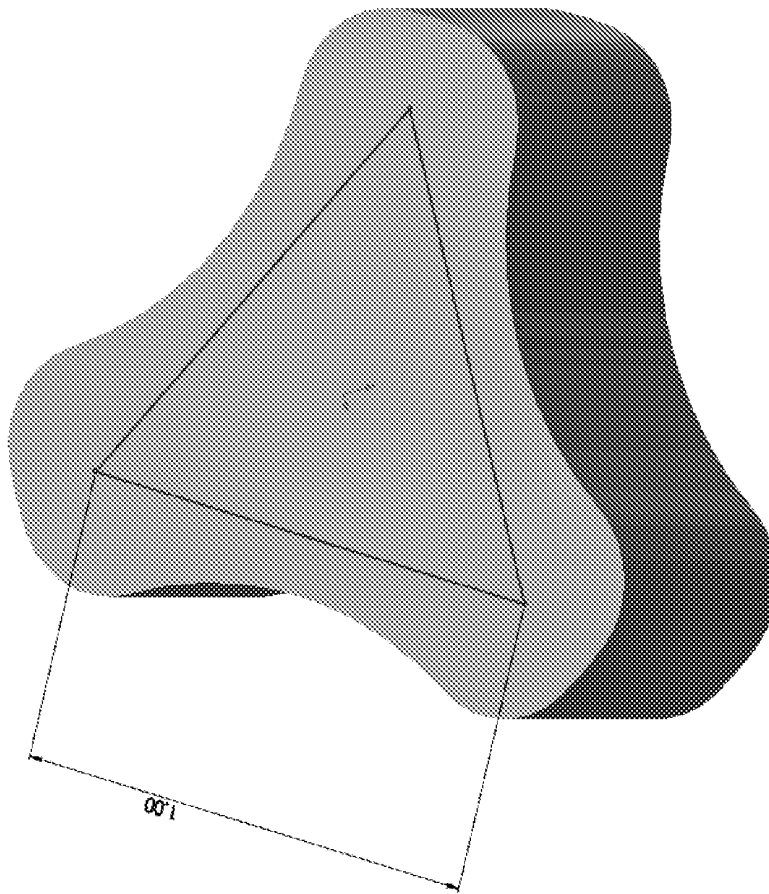
14. The dry powder inhalation composition of claim 13, wherein the bulking agent comprises trehalose dihydrate.
15. The dry powder inhalation composition of claim 13, wherein the wetting agent comprises polysorbate 80.
16. The dry powder inhalation composition of claim 13, wherein the hydrophobicity modifying agent comprises L-leucine.
17. The dry powder inhalation composition of claim 13, wherein the pH modifying agent comprises sodium citrate dihydrate.
18. The dry powder inhalation composition of claim 13, wherein the buffer comprises sodium chloride.
19. The dry powder inhalation composition of claim 13, wherein the composition comprises less than about 4 percent by weight water.
20. The dry powder inhalation composition of claim 13, wherein the composition comprises less than about 2 percent by weight water.
21. The dry powder inhalation composition of claim 13, wherein the composition comprises less than about 1 percent by weight water.
22. The dry powder inhalation composition of claim 13, wherein the dry powder particles comprise particles having a three dimensional shape including a width and length not less than 1 micrometer and not more than 2 micrometers and a depth not less than 0.3 micrometers and not more than 0.8 micrometers.
23. The dry powder inhalation composition of claim 13, wherein the dry powder particles comprise a dried solution comprising trehalose dihydrate, L-leucine, treprostinil sodium, polysorbate 80, sodium citrate dihydrate, sodium chloride and water.
24. The dry powder inhalation composition of claim 23, wherein the dry powder particles comprise by percent solids about 0.581 percent treprostinil sodium, about 92.32 percent trehalose, about 2.19 percent polysorbate 80, about 4.39 percent L-leucine, about 0.26 percent sodium citrate, and about 0.25 percent sodium chloride.
25. A method of making a particle for dry powder delivery to the lung of a patient in need thereof, comprising:

molding a composition comprising about 12.30 weight percent trehalose dihydrate, about 0.53 weight percent L-leucine, about 0.07 weight percent treprostinil sodium, about 0.26 weight percent polysorbate 80, about 0.04 weight percent sodium citrate dihydrate, about 0.03 weight percent sodium chloride and about 86.78 weight percent water into a particle; and

drying the composition such that the particle comprises less than 4 percent by weight water.

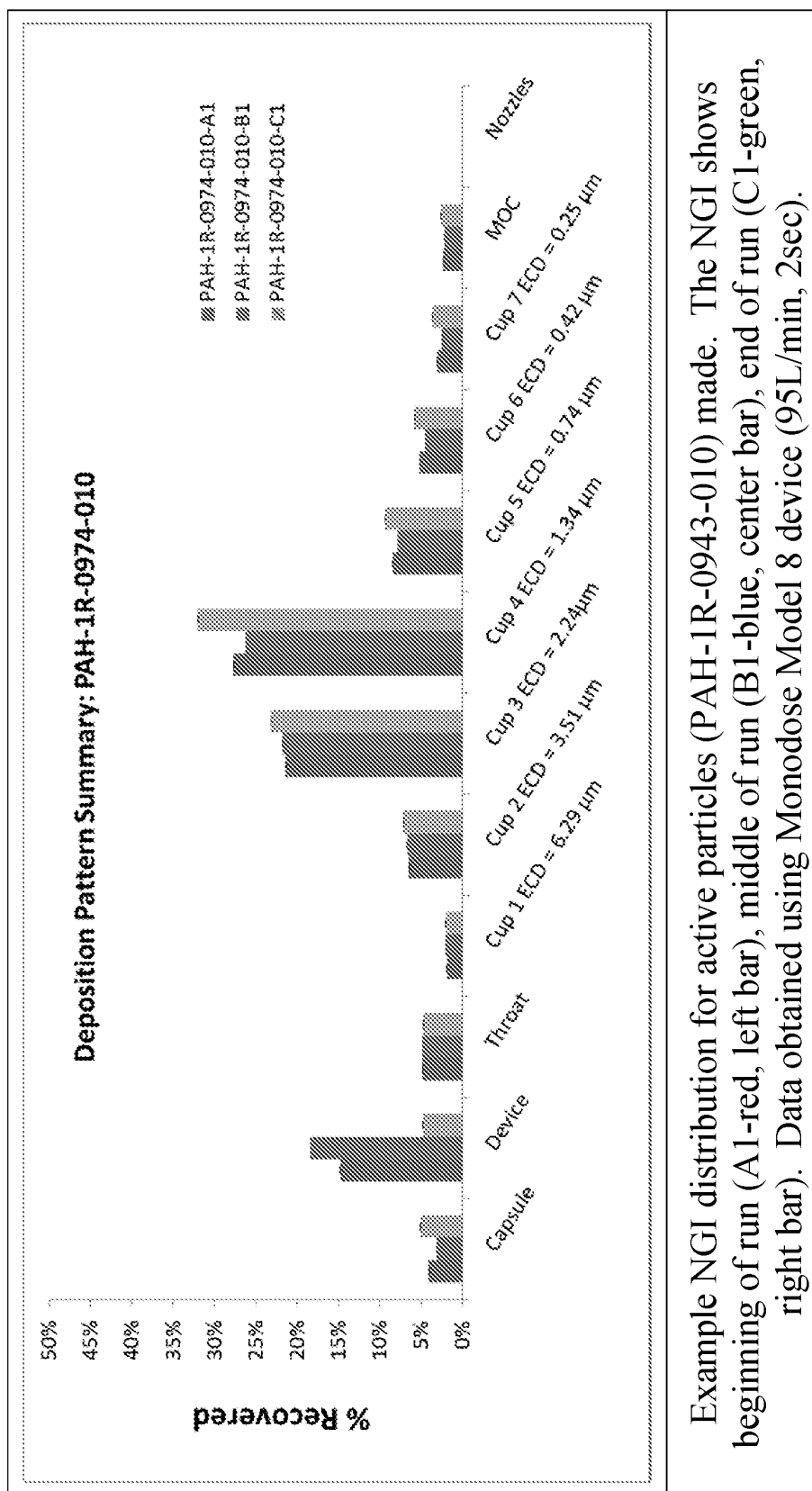
26. A method of treating a patient having pulmonary arterial hypertension, comprising:
delivering greater than 12.5 micrograms of treprostinil to a patient per breath.
27. A method of treating a patient having pulmonary arterial hypertension, comprising:
delivering greater than 25 micrograms of treprostinil to a patient per breath.

FIGURE 1



1 micrometer 'pollen' particle

FIGURE 2



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FIGURE 3A

		Time (h)																
		0.00	0.08	0.17	0.25	0.33	0.42	0.50	0.75	1.00	1.50	2.00	2.50	3.00	3.50	4.00	6.00	8.00
		Treprostinil (ng/mL)																
Cohort	Subject Alias																	
Cohort I	I-A	0.00	0.164	NR	0.166	0.197	0.150	0.146	0.0992	0.0553	0.0314	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	I-B	0.00	0.243	0.251	0.266	0.326	0.268	0.278	0.136	0.124	0.0688	0.0573	0.0292	0.0328	0.00	0.00	0.00	0.00
	I-C	0.00	0.200	0.272	0.412	0.414	0.251	0.176	0.139	0.108	0.0460	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	I-D	0.00	0.474	0.493	0.458	0.443	0.511	0.383	0.258	0.138	0.0629	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	I-E	0.00	0.200	0.28	0.224	0.255	0.172	0.148	0.114	0.105	0.0519	0.0308	0.00	0.00	0.00	0.00	0.00	0.00
	I-F	0.00	0.402	NR	0.456	0.427	0.313	0.265	0.188	0.106	0.0483	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	N	6	6	4	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	0.00	0.281	0.324	0.330	0.344	0.278	0.233	0.156	0.106	0.0516	0.0147	0.00487	0.00547	0.00	0.00	0.00	0.00
	SD	0.00	0.127	0.113	0.127	0.101	0.130	0.0934	0.0585	0.028	0.0132	0.0242	0.0119	0.0134	0.00	0.00	0.00	0.00
	Min	0.00	0.164	0.251	0.166	0.197	0.150	0.146	0.0992	0.0553	0.0314	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Median	0.00	0.222	0.276	0.339	0.370	0.260	0.221	0.138	0.107	0.0501	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Max	0.00	0.474	0.493	0.458	0.443	0.511	0.383	0.258	0.138	0.0688	0.0573	0.0292	0.0328	0.00	0.00	0.00	0.00
	CV%	NC	45.1	35.0	38.6	29.5	46.7	40.1	37.6	26.4	25.6	165.1	244.9	244.9	NC	NC	NC	NC

NC= Not calculated; NR = Not Reported

FIGURE 3B

Cohort	Subject Alias	C _{max} (ng/mL)	T _{max} (h)	t _{1/2} (h)	AUC _{last} (h*ng/mL)	AUC _{inf} (h*ng/mL)	CL/F (L/h)	V _z /F (L)
Cohort 1	1-A	0.197	0.33	0.454	0.146	0.167	150	98.2
	1-B	0.326	0.33	0.795	0.321	0.359	69.7	80.0
	1-C	0.414	0.33	0.460	0.242	0.272	91.8	60.9
	1-D	0.511	0.42	0.377	0.389	0.423	59.1	32.1
	1-E	0.280	0.17	0.648	0.218	0.247	101	94.7
	1-F	0.456	0.25	0.399	0.308	0.336	74.4	42.8
	N	6	6	6	6	6	6	6
	Mean	0.364	0.306	0.522	0.271	0.301	91.0	68.1
	SD	0.117	0.086	0.164	0.086	0.091	32.6	27.4
	Min	0.20	0.17	0.38	0.15	0.17	59.1	32.1
	Median	0.37	0.33	0.46	0.28	0.30	83.1	70.4
	Max	0.51	0.42	0.80	0.39	0.42	150	98.2
	CV%	32.3	28.2	31.5	31.8	30.2	35.8	40.2
	Geometric Mean	0.347	0.294	0.503	0.258	0.288	86.8	63.0
	CV% Geometric Mean	36.52	33.02	29.96	35.77	33.91	33.9	47.67

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FIGURE 4A

		Time (h)																	
		0.00	0.08	0.17	0.25	0.33	0.42	0.50	0.75	1.00	1.50	2.00	2.50	3.00	3.50	4.00	6.00	8.00	
Cohort	Subject Alias	Treprostinil (ng/mL)																	
Cohort 2	2-A	0.00	NR	0.99	0.93	0.77	0.70	0.58	0.37	0.30	0.12	0.08	0.03	0.00	0.00	0.00	0.00	0.00	
	2-B	0.00	0.94	1.03	0.95	0.83	0.64	0.41	0.30	0.18	0.09	0.05	0.03	0.03	0.00	0.00	0.00	0.00	
	2-C	0.00	0.48	0.41	0.32	0.31	0.26	0.22	0.13	0.08	0.04	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
	2-D	0.00	0.45	0.53	0.50	0.46	0.45	0.44	0.30	0.22	0.08	0.04	0.00	0.00	0.00	0.00	0.00	0.00	
	2-E	0.00	0.28	0.29	0.26	0.23	0.21	0.20	0.13	0.08	0.04	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
	2-F	0.00	0.00	0.09	0.11	0.11	0.12	0.11	0.06	0.03	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
	N	6	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	
	Mean	0.00	0.429	0.556	0.511	0.452	0.395	0.326	0.214	0.149	0.0624	0.0277	0.0108	0.00507	0.00	0.00	0.00	0.00	
	SD	0.00	0.342	0.382	0.355	0.295	0.240	0.180	0.123	0.101	0.0433	0.0333	0.0168	0.0124	0.00	0.00	0.00	0.00	
	Min	0.00	0.00	0.0853	0.111	0.108	0.116	0.110	0.0600	0.0270	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
	Median	0.00	0.453	0.470	0.410	0.385	0.351	0.313	0.216	0.134	0.0603	0.0186	0.00	0.00	0.00	0.00	0.00	0.00	
	Max	0.00	0.937	1.03	0.948	0.833	0.703	0.583	0.367	0.298	0.124	0.0794	0.0332	0.0304	0.00	0.00	0.00	0.00	
	CV%	NC	79.7	68.8	69.4	65.1	60.8	55.2	57.6	68.1	69.3	120.3	155.0	244.9	NC	NC	NC	NC	

NC= Not calculated; NR = Not Reported

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FIGURE 4B

Cohort	Subject	Cmax (ng/mL)	Tmax (h)	t _{1/2} (h)	AUClast (h*ng/mL)	AUCinf (h*ng/mL)	CL/F (L/h)	Vz/F (L)
Cohort 2	2-A	0.991	0.17	0.482	0.723	0.746	67.0	46.6
	2-B	1.03	0.17	0.624	0.663	0.690	72.5	65.2
	2-C	0.477	0.08	0.474	0.254	0.282	177	121
	2-D	0.530	0.17	0.410	0.466	0.488	102	60.5
	2-E	0.288	0.17	0.478	0.212	0.242	206	142
	2-F	0.116	0.42	0.247	0.0706	0.0802	624	222
	N	6	6	6	6	6	6	6
	Mean	0.572	0.195	0.452	0.398	0.422	208	110
	SD	0.370	0.114	0.123	0.262	0.265	211	66.6
	Min	0.116	0.0830	0.247	0.0706	0.0802	67.0	46.6
	Median	0.504	0.167	0.476	0.360	0.385	140	93.3
	Max	1.03	0.417	0.624	0.723	0.746	624	222
	CV%	64.7	58.6	27.2	65.8	62.8	101.5	60.7
	Geometric Mean	0.453	0.173	0.436	0.308	0.334	150	94.3
	CV% Geometric Mean	98.2	54.9	31.8	107.4	100.4	100.4	65.7

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FIGURE 5A

		NTime (h)																	
	Subject Cohort	Alias	Treprostinil (ng/mL)																
	Cohort 3	3-A	0.00	0.63	0.62	0.55	0.47	0.43	0.42	0.32	0.21	0.11	0.06	0.03	0.00	0.00	0.00	0.00	
		3-B	0.00	0.44	0.52	0.51	0.51	0.53	0.47	0.39	0.26	0.13	0.12	0.03	0.00	0.00	0.00	0.00	
		3-C	0.00	0.75	1.07	1.11	1.01	NR	0.80	0.47	0.35	0.14	0.07	0.05	0.03	0.00	0.00	0.00	
		3-D	0.00	NR	0.40	0.43	0.40	0.37	0.34	0.29	0.20	0.10	0.05	0.00	0.00	0.00	0.00	0.00	
		3-E	0.00	0.45	0.52	0.54	0.57	0.54	0.48	0.36	0.28	0.15	0.11	0.03	0.00	0.00	0.00	0.00	
		3-F	0.00	0.94	1.05	1.10	1.10	1.07	1.03	0.80	0.53	0.30	0.15	0.07	0.04	0.00	0.00	0.00	
		N	6	5	6	6	6	5	6	6	6	6	6	6	6	6	6	6	
		Mean	0.00	0.641	0.697	0.706	0.677	0.587	0.591	0.437	0.304	0.155	0.0951	0.0349	0.0124	0.00	0.00	0.00	
		SD	0.00	0.209	0.290	0.312	0.299	0.279	0.267	0.187	0.123	0.0755	0.0389	0.0225	0.0192	0.00	0.00	0.00	
		Min	0.00	0.437	0.399	0.428	0.400	0.371	0.344	0.285	0.199	0.0976	0.0547	0.00	0.00	0.00	0.00	0.00	
		Median	0.00	0.630	0.571	0.545	0.540	0.532	0.474	0.379	0.269	0.136	0.0916	0.0342	0.00	0.00	0.00	0.00	
		Max	0.00	0.936	1.07	1.11	1.10	1.07	1.03	0.796	0.529	0.304	0.149	0.0682	0.0395	0.00	0.00	0.00	
		CV%	NC	32.6	41.7	44.2	44.2	47.5	45.2	42.8	40.5	48.8	40.9	64.6	155.4	NC	NC	NC	

NC= Not calculated; NR = Not Reported

FIGURE 5B

Cohort	Subject Alias	Cmax (ng/mL)	Tmax (h)	t _{1/2} (h)	AUClast (h*ng/mL)	AUCinf (h*ng/mL)	CL/F (L/h)	Vz/F (L)
Cohort 3	3-A	0.630	0.08	0.609	0.538	0.568	132	116
	3-B	0.532	0.42	0.568	0.611	0.638	118	96.3
	3-C	1.11	0.25	0.980	0.906	0.955	78.5	111
	3-D	0.428	0.25	0.522	0.411	0.452	166	125
	3-E	0.567	0.33	0.531	0.619	0.639	117	89.9
	3-F	1.10	0.25	0.520	1.26	1.29	58.1	43.6
	N	6	6	6	6	6	6	6
	Mean	0.728	0.264	0.622	0.724	0.757	112	97.0
	SD	0.299	0.111	0.179	0.309	0.310	38.5	29.1
	Min	0.428	0.0833	0.520	0.411	0.452	58.1	43.6
	Median	0.599	0.250	0.550	0.615	0.639	117	104
	Max	1.11	0.417	0.980	1.26	1.29	166	125
	CV%	41.1	42.0	28.7	42.7	41.0	34.5	30.0
	Geometric Mean	0.681	0.238	0.605	0.676	0.711	106	92.1
	CV% Geometric Mean	41.2	60.0	24.8	41.5	39.4	39.4	40.0

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FIGURE 6A

		NTime (h)																
		0.00	0.08	0.17	0.25	0.33	0.42	0.50	0.75	1.00	1.50	2.00	2.50	3.00	3.50	4.00	6.00	8.00
	Subject	Trepstinil (ng/mL)																
Cohort 4	4-A	0.00	0.294	0.534	0.648	0.684	0.722	0.763	0.575	0.358	0.150	0.0789	0.0523	0.0332	0.00	0.00	0.00	0.00
	4-B	0.00	0.629	0.872	0.959	1.04	1.02	0.924	0.622	0.495	0.273	0.144	0.0710	0.0449	0.0300	0.00	0.00	0.00
	4-C	0.00	0.552	0.725	0.704	0.718	0.688	0.729	0.625	0.557	0.346	0.205	0.143	0.0908	0.0445	0.0286	0.00	0.00
	4-D	0.00	1.30	1.54	1.44	1.35	1.29	1.08	0.790	0.559	0.290	0.134	0.0709	0.0728	0.0333	0.00	0.00	0.00
	4-E	0.00	0.877	1.14	1.16	1.14	0.969	0.970	0.657	0.513	0.270	0.166	0.0968	0.0524	0.0367	0.0256	0.00	0.00
	4-F	0.00	1.13	1.21	1.23	1.09	0.915	0.826	0.662	0.521	0.253	0.125	0.140	0.0698	0.0324	0.0837	0.00	0.00
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	0.00	0.797	1.00	1.02	1.00	0.934	0.882	0.655	0.501	0.264	0.142	0.0957	0.0607	0.0295	0.0230	0.00	0.00
	SD	0.00	0.377	0.365	0.310	0.257	0.220	0.134	0.0730	0.0742	0.0642	0.0422	0.0382	0.0210	0.0153	0.0326	0.00	0.00
	Min	0.00	0.294	0.534	0.648	0.684	0.688	0.729	0.575	0.358	0.150	0.0789	0.0523	0.0332	0.00	0.00	0.00	0.00
	Median	0.00	0.753	1.01	1.06	1.07	0.942	0.875	0.641	0.517	0.272	0.139	0.0839	0.0611	0.0329	0.0128	0.00	0.00
	Max	0.00	1.30	1.54	1.44	1.35	1.29	1.08	0.790	0.559	0.346	0.205	0.143	0.0908	0.0445	0.0837	0.00	0.00
	CV%	NC	47.3	36.3	30.3	25.6	23.5	15.2	11.1	14.8	24.4	29.7	40.0	34.7	51.9	141.8	NC	NC

NC= Not calculated

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FIGURE 6B

Cohort	Subject	Cmax (ng/mL)	Tmax (h)	t_{1/2} (h)	AUClast (h*ng/mL)	AUCinf (h*ng/mL)	CL/F (L/h)	Vz/F (L)
Cohort 4	4-A	0.763	0.50	0.801	0.781	0.819	122	141
	4-B	1.04	0.33	0.805	1.13	1.17	85.8	99.6
	4-C	0.729	0.50	0.702	1.18	1.21	82.8	83.8
	4-D	1.54	0.17	0.583	1.44	1.46	68.3	57.4
	4-E	1.16	0.25	0.968	1.26	1.30	77.1	108
	4-F	1.23	0.25	0.794	1.28	1.37	72.8	83.4
	N	6	6	6	6	6	6	6
	Mean	1.08	0.333	0.775	1.18	1.22	84.8	95.5
	SD	0.305	0.139	0.127	0.221	0.225	19.3	28.2
	Min	0.729	0.167	0.583	0.781	0.819	68.3	57.4
	Median	1.10	0.292	0.798	1.22	1.25	79.9	91.7
	Max	1.54	0.500	0.968	1.44	1.46	122	141
	CV%	28.3	41.8	16.4	18.7	18.4	22.8	29.5
	Geometric Mean	1.04	0.309	0.766	1.16	1.20	83.2	92.0
	CV%							
	Geometric Mean	29.5	45.5	17.0	21.2	20.7	20.7	30.8

FIGURE 7A

		NTime (h)																	
		0.00	0.08	0.17	0.25	0.33	0.42	0.50	0.75	1.00	1.50	2.00	2.50	3.00	3.50	4.00	6.00	8.00	
Cohort	Subject	Trepstinil (ng/mL)																	
Cohort 5	5-A	0.00	1.13	1.96	1.80	1.64	1.54	1.38	0.971	0.752	0.394	0.238	0.136	0.0833	0.0583	0.0345	0.00	0.00	
	5-B	0.00	0.562	1.26	1.26	1.45	1.40	1.24	0.876	0.605	0.312	0.195	0.0732	0.0351	0.00	0.00	0.00	0.00	
	5-C	0.00	0.478	0.763	0.979	1.02	0.976	0.909	NR	0.409	0.294	0.128	0.0658	0.0433	0.00	0.00	0.00	0.00	
	5-D	0.00	1.04	1.42	1.26	1.08	1.02	0.824	0.635	0.467	0.252	0.146	0.0615	0.0304	0.00	0.00	0.00	0.00	
	5-E	0.00	0.543	0.728	0.730	0.743	0.754	0.699	0.502	0.397	0.230	0.113	0.0500	0.0262	0.00	0.00	0.00	0.00	
	5-F	0.00	0.502	0.510	0.427	0.399	0.333	0.265	0.201	0.120	0.0565	0.0306	0.00	0.00	0.00	0.00	0.00	0.00	
N		6	6	6	6	6	6	6	5	6	6	6	6	6	6	6	6	6	6
Mean		0.00	0.709	1.11	1.08	1.06	1.00	0.886	0.637	0.458	0.256	0.142	0.0644	0.0364	0.00972	0.00575	0.00	0.00	
SD		0.00	0.294	0.542	0.478	0.453	0.438	0.399	0.307	0.214	0.113	0.0714	0.0437	0.0273	0.0238	0.0141	0.00	0.00	
Min		0.00	0.478	0.510	0.427	0.399	0.333	0.265	0.201	0.120	0.0565	0.0306	0.00	0.00	0.00	0.00	0.00	0.00	
Median		0.00	0.553	1.01	1.12	1.05	0.998	0.867	0.635	0.438	0.273	0.137	0.0637	0.0328	0.00	0.00	0.00	0.00	
Max		0.00	1.13	1.96	1.80	1.64	1.54	1.38	0.971	0.752	0.394	0.238	0.136	0.0833	0.0583	0.0345	0.00	0.00	
CV%		NC	41.5	48.9	44.4	43.0	43.6	45.0	48.2	46.6	44.2	50.4	67.9	74.9	244.9	244.9	NC	NC	

NC= Not calculated, NR = Not Reported

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FIGURE 7B

Cohort	Subject	Cmax (ng/mL)	Tmax (h)	t _{1/2} (h)	AUClast (h*ng/mL)	AUCinf (h*ng/mL)	CL/F (L/h)	Vz/F (L)
Cohort 5	5-A	1.96	0.17	0.647	1.87	1.90	65.7	61.3
	5-B	1.45	0.33	0.495	1.42	1.45	86.2	61.6
	5-C	1.02	0.33	0.561	1.05	1.08	115	93.3
	5-D	1.42	0.17	0.526	1.18	1.20	104	78.9
	5-E	0.754	0.42	0.473	0.874	0.891	140	95.6
	5-F	0.510	0.17	0.448	0.352	0.372	336	217
	N	6	6	6	6	6	6	6
	Mean	1.19	0.264	0.525	1.12	1.15	141	101
	SD	0.528	0.111	0.0716	0.512	0.516	98.8	58.7
	Min	0.510	0.167	0.448	0.352	0.372	65.7	61.3
	Median	1.22	0.250	0.511	1.11	1.14	110	86.1
	Max	1.96	0.417	0.647	1.87	1.90	336	217
	CV%	44.5	42.0	13.6	45.6	44.9	69.9	57.9
	Geometric Mean	1.08	0.245	0.521	1.00	1.03	121	91.3
	CV%							
	Geometric Mean	52.4	44.9	13.2	62.6	60.9	60.9	49.3

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FIGURE 8A

		NTime (h)																
		0.00	0.08	0.17	0.25	0.33	0.42	0.50	0.75	1.00	1.50	2.00	2.50	3.00	3.50	4.00	6.00	8.00
Cohort	Subject	Trepstinil (ng/mL)																
Cohort 6-R	6-A	0.00	0.244	0.474	0.596	0.622	0.704	0.61	0.459	0.345	0.177	0.085	0.0387	0.00	0.00	0.00	0.00	0.00
	6-B	0.00	0.877	0.907	0.75	0.657	0.538	0.459	0.287	0.166	0.0915	0.0488	0.00	0.00	0.00	0.00	0.00	0.00
	6-C	0.00	0.547	1.47	1.68	1.67	1.59	1.41	1.00	0.762	0.406	0.232	0.144	0.0885	0.0603	0.0376	0.00	0.00
	6-D	0.00	1.41	1.7	1.89	1.86	1.75	1.69	1.24	0.9	0.463	0.22	0.116	0.0673	0.0758	0.0404	0.00	0.00
	6-E	0.00	1.21	1.83	2.12	2.34	2.06	1.9	1.65	1.25	0.699	0.431	0.244	0.14	0.106	0.093	0.00	0.00
	6-F	0.00	0.615	0.938	1.09	1.19	1.12	1.11	0.912	0.682	0.412	0.207	0.122	0.0677	0.0502	0.0325	0.00	0.00
N		6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean		0.00	0.817	1.22	1.35	1.39	1.29	1.2	0.925	0.684	0.375	0.204	0.111	0.0606	0.0487	0.0339	0.00	0.00
SD		0.00	0.436	0.529	0.631	0.688	0.605	0.58	0.501	0.389	0.217	0.135	0.0854	0.0539	0.0422	0.0342	0.00	0.00
Min		0.00	0.244	0.474	0.596	0.622	0.538	0.459	0.287	0.166	0.0915	0.0488	0.00	0.00	0.00	0.00	0.00	0.00
Median		0.00	0.746	1.20	1.39	1.43	1.36	1.26	0.956	0.722	0.409	0.214	0.119	0.0675	0.0553	0.0351	0.00	0.00
Max		0.00	1.41	1.83	2.12	2.34	2.06	1.90	1.65	1.25	0.699	0.431	0.244	0.14	0.106	0.093	0.00	0.00
CV%		NC	53.4	43.4	46.6	49.5	46.8	48.4	54.2	56.8	57.8	66.1	77.1	89	86.6	100.8	NC	NC

NC= Not calculated; NR = Not Reported

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FIGURE 8B

Cohort	Subject	Cmax (ng/mL)	Tmax (h)	t _{1/2} (h)	AUClast (h*ng/mL)	AUCinf (h*ng/mL)	CL/F (L/h)	Vz/F (L)
Cohort 6-R	6-A	0.704	0.42	0.456	0.696	0.721	208	137
	6-B	0.907	0.17	0.566	0.573	0.613	245	200
	6-C	1.68	0.25	0.768	1.80	1.85	81.3	90.1
	6-E	1.89	0.25	0.628	2.10	2.13	70.3	63.6
	6-F	2.34	0.33	0.734	2.80	2.90	51.8	54.9
	6-G	1.19	0.33	0.665	1.50	1.53	97.9	93.8
	N	6	6	6	6	6	6	6
	Mean	1.45	0.292	0.636	1.58	1.62	126	107
	SD	0.626	0.087	0.114	0.849	0.869	80.3	54.0
	Min	0.704	0.167	0.456	0.573	0.613	51.8	54.9
	Median	1.44	0.292	0.646	1.65	1.69	89.6	92.0
	Max	2.34	0.417	0.768	2.8	2.90	245	200
	CV%	43.1	30.0	18.0	53.8	53.5	63.9	50.7
	Geometric Mean	1.33	0.28	0.627	1.36	1.41	107	96.5
	CV% Geometric Mean	48.6	32.9	19.2	70	68.3	68.3	50.9

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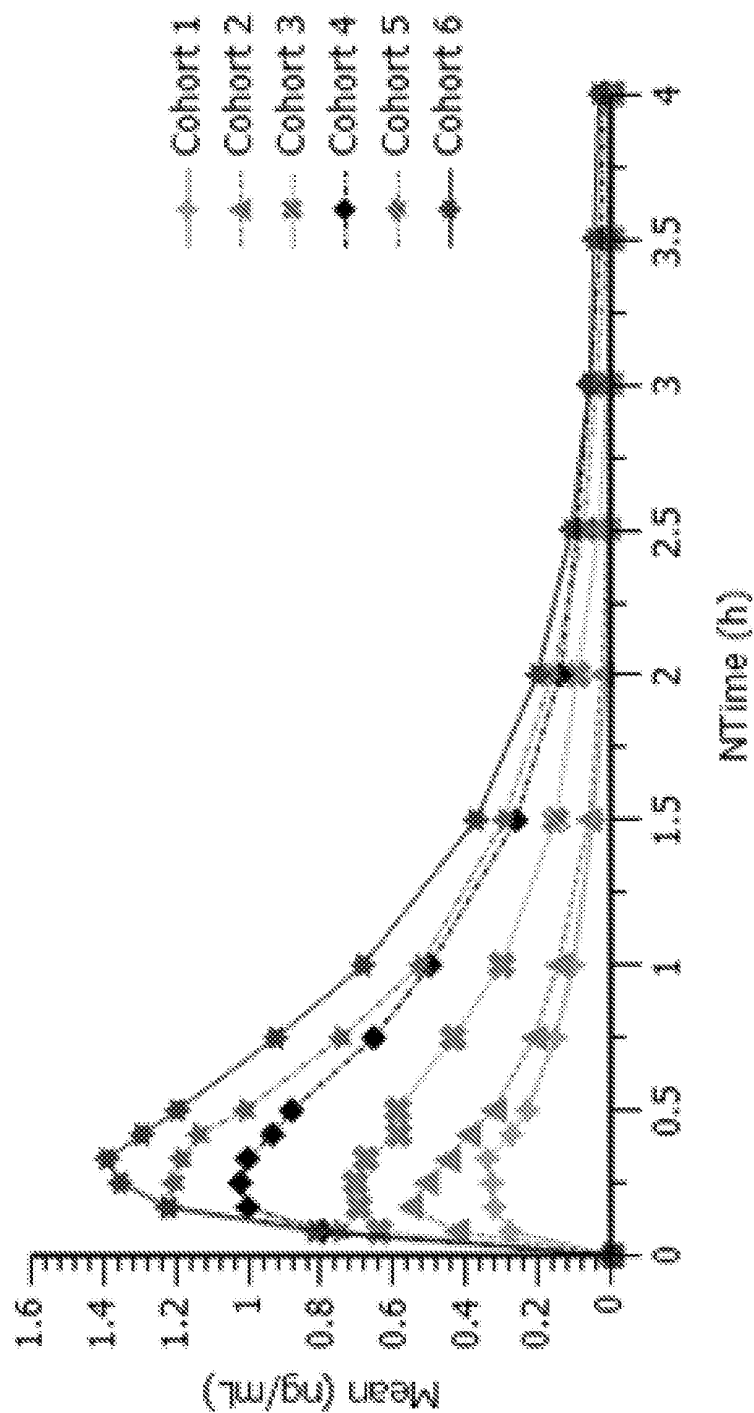
PCT/US2017/031301

FIGURE 8C

Cohort	Subject	Cmax (ng/mL)	Tmax (h)	t½ (h)	AUClast (h*ng/mL)	AUCinf (h*ng/mL)	CL/F (L/h)	Vz/F (L)
Cohort 6 - Original	6-A (ORIGINAL)	1.55	0.33	0.607	1.96	1.99	75.6	66.2
	6-B (ORIGINAL)	1.16	0.08	0.946	0.868	0.987	152	208
	6-C (ORIGINAL)	1.17	0.42	0.534	1.28	1.30	115	88.9
	6-D (ORIGINAL)	0.968	0.42	0.649	1.30	1.33	113	105
	6-E (ORIGINAL)	1.55	0.17	0.658	1.68	1.71	87.9	83.5
	6-F (ORIGINAL)	0.835	0.25	0.565	0.871	0.891	168	137
	N	6	6	6	6	6	6	6
	Mean	1.21	0.278	0.660	1.33	1.37	119	115
	SD	0.295	0.136	0.148	0.435	0.418	35.8	51.4
	Min	0.835	0.0833	0.534	0.868	0.891	75.6	66.2
	Median	1.17	0.292	0.628	1.29	1.32	114	97.2
	Max	1.55	0.417	0.946	1.96	1.99	168	208
	CV%	24.4	49.0	22.5	32.8	30.6	30.2	44.8
	Geometric Mean CV%	1.18	0.242	0.648	1.27	1.31	114	107
	Geometric Mean	25.2	69.5	20.4	34.2	31.4	31.4	42.4

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FIGURE 8D



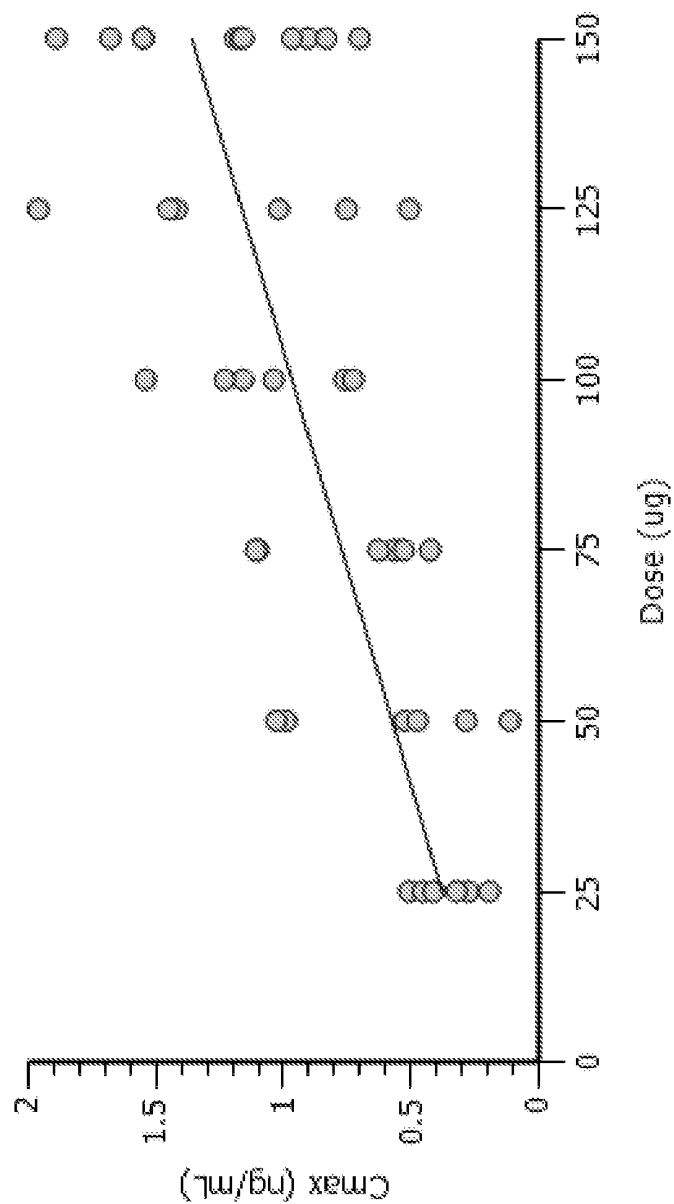
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FIGURE 8E

$Rsq = 0.4785$, Intercept = 0.185, Slope = 0.007835



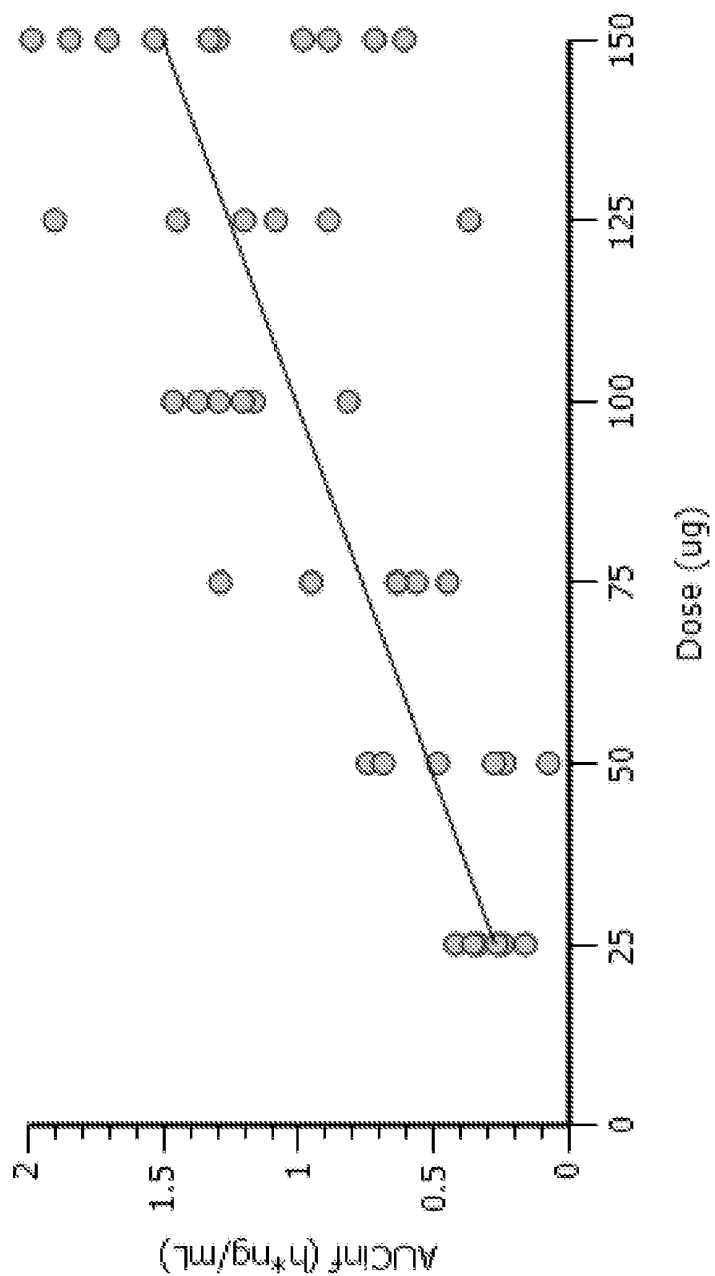
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FIGURE 8F

$Rsq = 0.5172$, Intercept = 0.03113, Slope = 0.009813



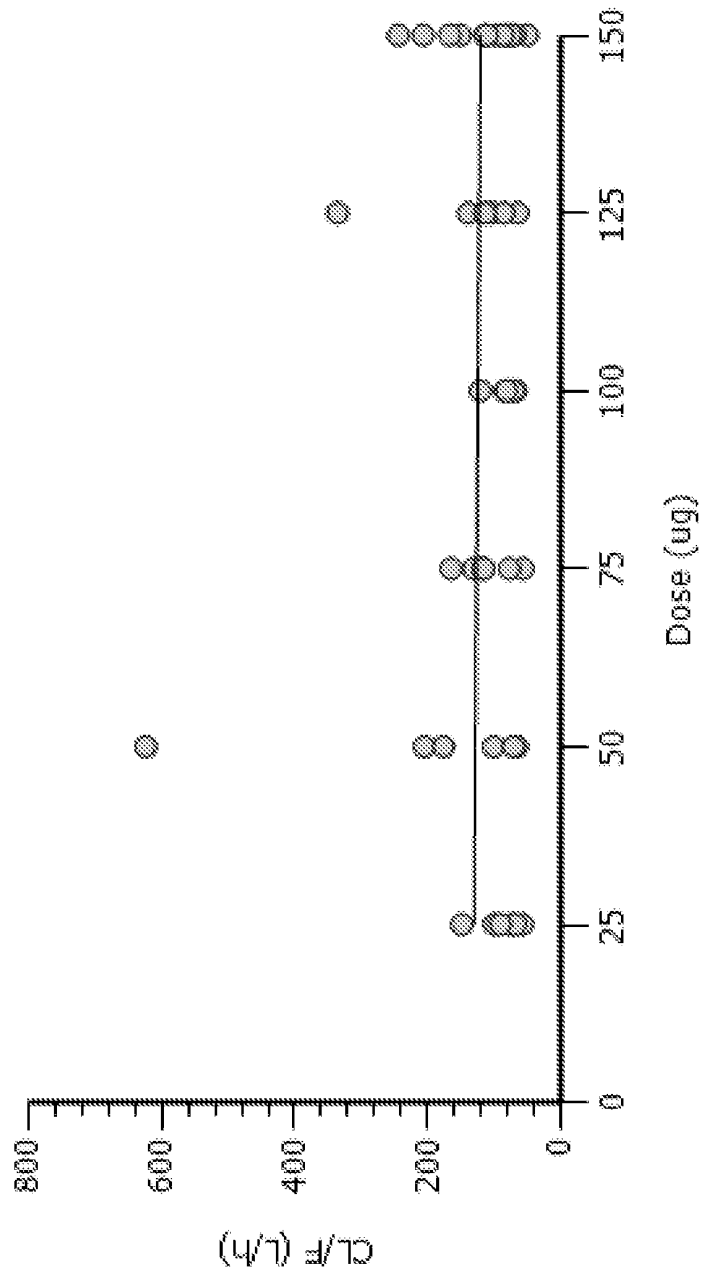
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FIGURE 8G

$Rsq = 0.001393$, Intercept = 133.5, Slope = -0.07923



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FIGURE 9

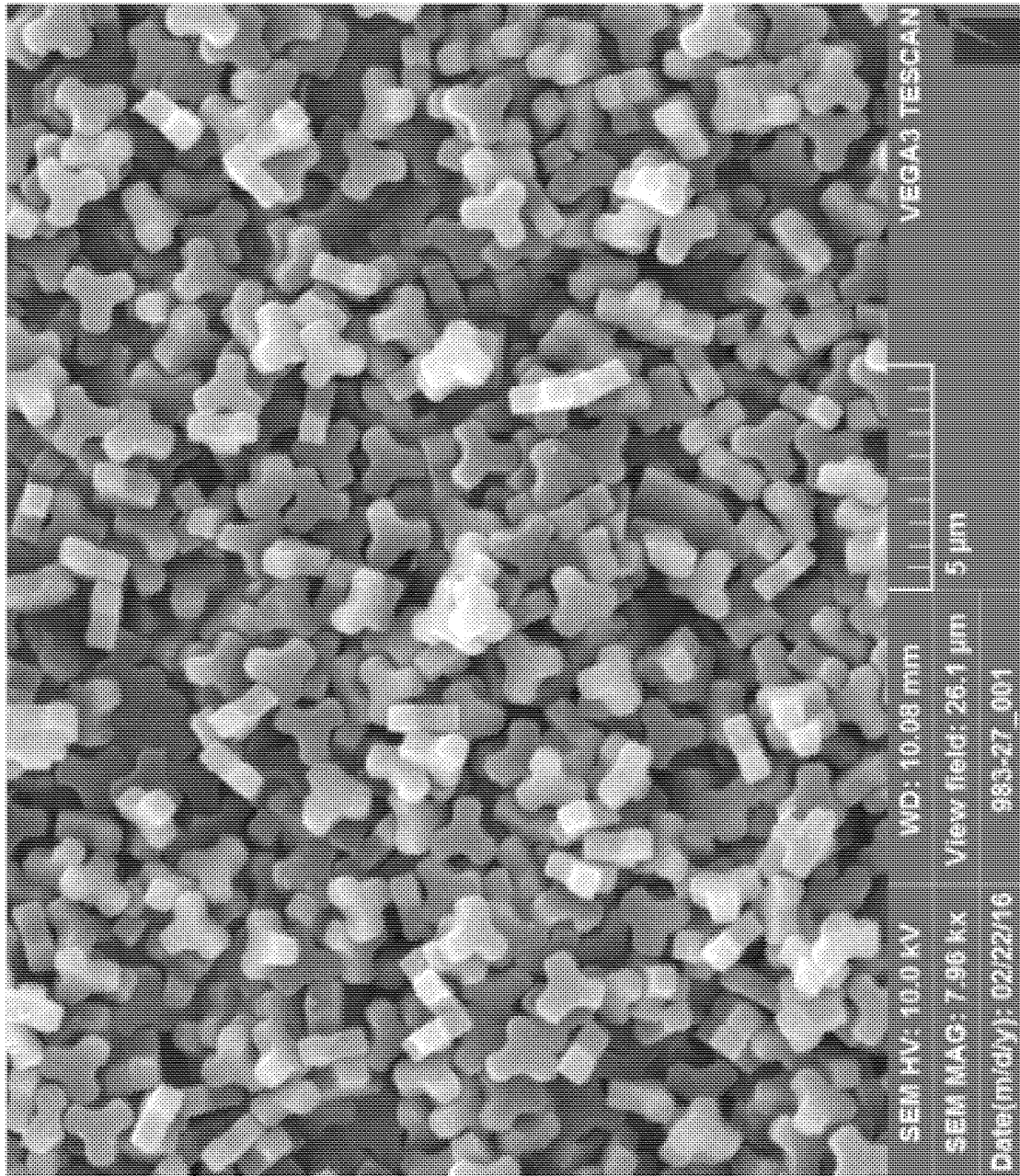


FIGURE 10

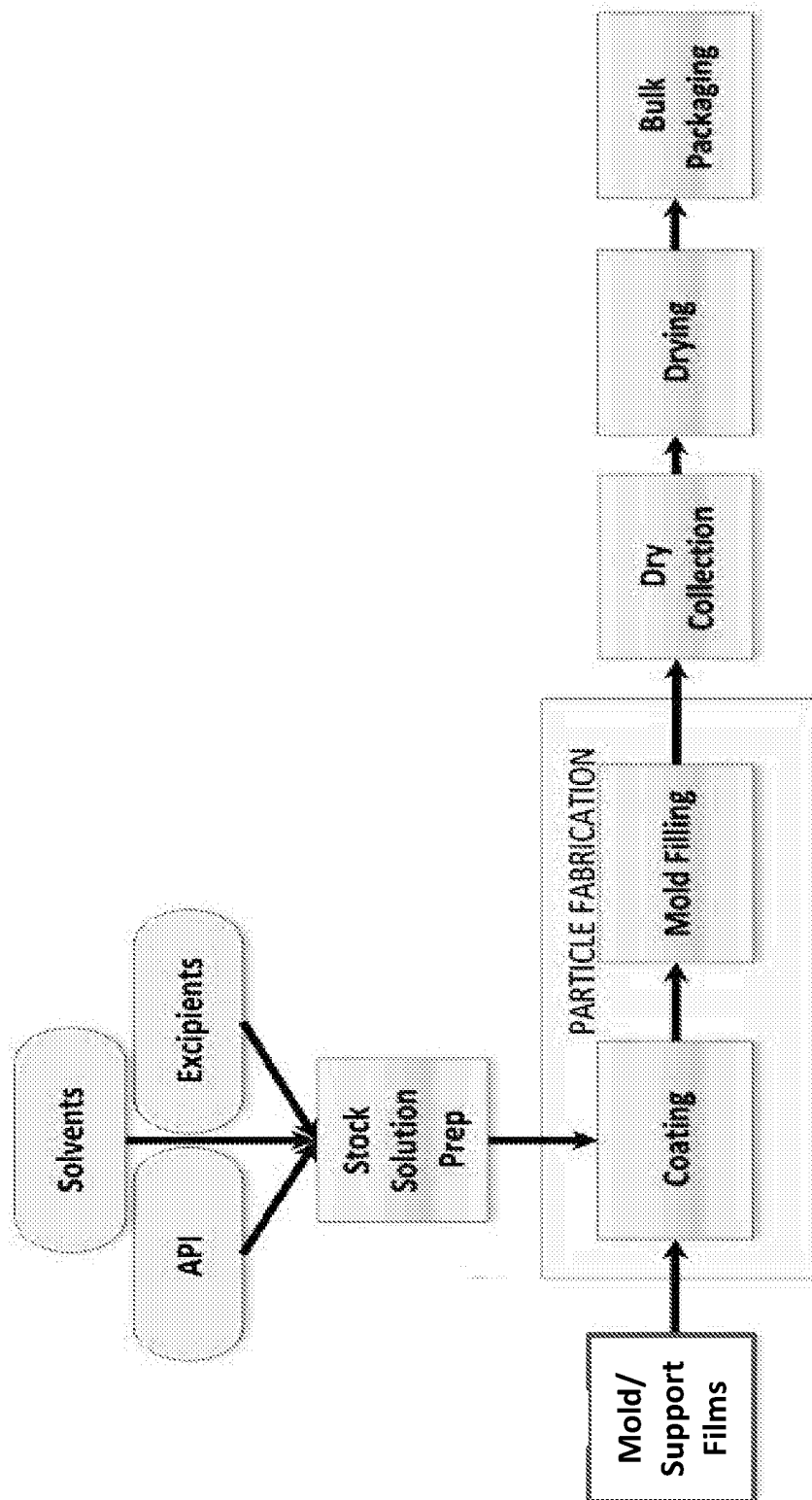
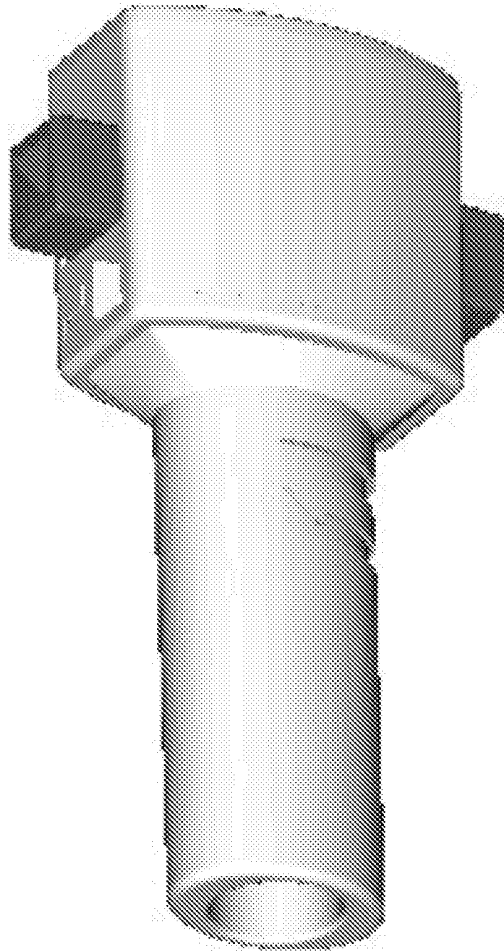


FIGURE 11



RS00 Model 8 Dry Powder Inhalation Device

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2017/031301

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61P 9/12; A61K 9/72; A61K 31/00; A61K 31/192; A61K 31/557; A61P 9/00 (2017.01)

CPC - A61K 31/5575; A61K 9/00; A61K 9/0075; A61K 31/00; A61K 31/192; A61K 31/557 (2017.05)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2009/0036465 A1 (ROSCIGNO et al) 05 February 2009 (05.02.2009) entire document	1-21, 23, 26, 27
Y	US 2009/0264389 A1 (ZENG) 22 October 2009 (22.10.2009) entire document	1-12
Y	US 2016/0045434 A1 (ERATECH SRL) 18 February 2016 (18.02.2016) entire document	13-21, 23
Y	US 2014/0127227 A1 (CHANG) 08 May 2014 (08.05.2014) entire document	13-21, 23
Y	US 5,441,060 A (ROSE et al) 15 August 1995 (15.08.1995) entire document	26, 27

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

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Date of the actual completion of the international search

28 June 2017

Date of mailing of the international search report

19 JUL 2017

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(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: COMPOSITION AND METHOD FOR INHALATION

(57) Abstract: A prostaglandin composition and method for treating pulmonary arterial hypertension is disclose. The composition is based on diketopiperazine for pulmonary inhalation.

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COMPOSITION AND METHOD FOR INHALATION

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application Serial No. 62/682,109, filed on June 7, 2018, the entire contents of which are incorporated herein by reference.

TECHNICAL FIELD

[0002] Compositions and methods for treating pulmonary arterial hypertension are disclosed.

BACKGROUND

[0003] Pulmonary arterial hypertension (PAH) is a complex, multifactorial, progressive syndrome characterized by persistent elevation of pulmonary artery pressure and pulmonary vascular resistance (PVR) that leads to increase in right ventricular afterload and eventually culminates in right heart failure. Right ventricular failure limits cardiac output during exertion. The most common symptom at presentation is breathlessness, fatigue, angina, syncope, and abdominal distension, with impaired exercise capacity as a hallmark of the disease.

[0004] The symptoms of PAH are non-specific. The symptoms at rest are reported only in very advanced cases due to the non-specific nature of the symptoms, there is a substantial delay of more than 2 years in the diagnosis of pulmonary hypertension (PH). Unfortunately approximately 70% of the patients with PH are diagnosed when they have reached an advanced stage of disease (World Health Organization (WHO) Functional Class III and IV). Early identification and treatment of pulmonary hypertension (PH) is generally suggested because advanced disease may be less responsive to therapy. Treatment begins with a baseline assessment of disease severity, followed by primary therapy.

[0005] Assessing patients with pulmonary hypertension involves evaluating the severity of their disease using a range of clinical assessments, exercise tests, detection of specific biochemical markers, and echocardiographic and hemodynamic assessments. The clinical assessment of the patient has a pivotal role in the choice of the initial treatment, the evaluation of the response to therapy, and the possible escalation of therapy if needed.

[0006] PAH is classified into five groups (1-5) depending on the severity of the disease. In group 1, for example, the disease is heritable and commonly induced by drugs and toxins. PAH includes idiopathic pulmonary arterial hypertension (IPAH, formerly called primary pulmonary hypertension), hereditary PAH, or PAH due to diseases such as connective tissue

diseases, HIV infection, portal hypertension, congenital heart disease, schistosomiasis, and drug or toxin exposure (e.g. anorexigens). Estimated prevalence PAH is 15-50 cases per million, in the USA and Europe. However, the prevalence of PAH in certain at-risk groups is substantially higher. For example, in HIV-infected patients the prevalence of PAH is 0.5%, in patients with collagen vascular disorders it has been reported to be 7-12%, and in patients with sickle cell disease the prevalence is around 2-3.75%. In patients with hepatosplenic schistosomiasis 5% may have PAH. It is estimated that 10% of adults with congenital heart disease (CHD) may also have PAH. PAH in the newborn, known as persistent pulmonary hypertension of the newborn has been estimated to occur in 0.2% of live-born term infants.

[0007] Group 2 patients develop PH due to left heart disease from, inter alia, left ventricular systolic dysfunction, left ventricular diastolic dysfunction, valvular disease, or congenital/acquired left heart inflow/outflow tract obstruction, and congenital cardiomyopathies. In group 3, the PH is due to chronic lung disease and/or hypoxia exhibiting chronic obstructive pulmonary disease, interstitial lung disease, other pulmonary diseases with mixed restrictive and obstructive pattern, sleep-disordered breathing, alveolar hypoventilation disorders, chronic exposure to high altitude and developmental lung diseases. In group 4, PH is due to chronic thromboembolic pulmonary hypertension and group 5 patients exhibit PH due to unclear multifactorial mechanisms, including hematologic disorders such as chronic hemolytic anemia, myeloproliferative disorders, splenectomy; systemic disorders such as sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis; metabolic disorders, including glycogen storage disease, Gaucher's disease and thyroid disorders; and other disorders such as tumor/mass obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH.

[0008] Primary therapy is directed at the underlying cause of the PH and is warranted in nearly all patients with PH. The disease severity should be reassessed following primary therapy, in order to determine whether advanced therapy is indicated. Advanced therapy is directed at the pulmonary hypertension itself, rather than the underlying cause of the PH. Advanced therapy is widely accepted for many patients with group 1 pulmonary arterial hypertension (PAH). In contrast, it should only be administered on a case-by-case basis for patients with group 3 PH, group 4 PH, or group 5 PH, after carefully weighing the risks versus the benefits. Advanced therapy should not be administered to most patients with group 2 PH.

[0009] Until 2001, the only drug available to treat PAH was epoprostenol (Flolan, GlaxoSmithKline Pharmaceuticals), and it was mostly used as a bridge to transplantation. Since

then, other therapies have evolved, and as a result the prognosis of patients with PAH has significantly improved.

[0010] The clinical assessment of the patient has a pivotal role in the choice of the initial treatment, the evaluation of the response to therapy, and the possible escalation of therapy if needed. As mentioned above, diagnosing patients with pulmonary hypertension involves evaluating the severity of their disease using a range of clinical assessments, exercise tests, identification of biochemical markers, echocardiographic and hemodynamic assessments.

[0011] The clinical severity of PAH is classified according to a system originally developed for heart failure by the New York Heart Association (NYHA) and then modified by WHO for patients with PH. This functional classification (I-IV) system links symptoms with activity limitations, and allows clinicians to quickly predict disease progression and prognosis, as well as the need for specific treatment regimens, irrespective of the underlying etiology of PAH. Class I patients exhibit PH, but without resulting limitation of physical activity, and ordinary physical activity does not cause dyspnea or fatigue, chest pain, or near syncope. Class II patients exhibit pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest and ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope. Class III are patients with pulmonary hypertension resulting in marked limitation of physical activity, they are comfortable at rest and less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope. Class IV are patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest, and discomfort is increased by any physical activity.

[0012] The pathogenesis of PH is complex and many biochemical pathways and cell types have been identified or proposed as contributing to this vasoconstriction and vascular remodeling. These include altered synthesis of nitric oxide (NO), prostacyclin (PGI) and endothelin (ET-1), impaired potassium channel and growth factor receptor function, altered serotonin transporter regulation, increased oxidant stress, and enhanced matrix production of vasoactive factors, calcium signaling molecules, inflammatory mediators, growth factors, bone morphogenetic protein receptor 2 (BMPR2) mutations. However, the relative importance of each of these processes is unknown.

[0013] Clinical and preclinical studies strongly suggest that the pulmonary vascular endothelium plays a critical role and interactions between pulmonary endothelial cells with pulmonary arterial smooth muscle cells, and pulmonary pericytes plays a critical role in either

initiation and/or perpetuation of the characteristic progressive pulmonary arterial obstruction in PAH. Pulmonary vascular endothelium is a critical local source of several key mediators for vascular remodeling, including growth factors (fibroblast growth factor [FGF]-2, serotonin [5-HT], angiotensin II, and vasoactive peptides (NO, PGI₂, ET-1), cytokines (IL-1, IL-6, macrophage migration inhibitory factor [MIF]), and chemokines (monocyte chemoattractant protein [MCP]-1), adipokines (leptin). Endothelial dysfunction, is believed to occur early in disease and this leads to chronically impaired production of vasodilator and antiproliferative agents such as NO and prostacyclin, along with overexpression of vasoconstrictor and proliferative substances such as thromboxane A₂ and endothelin-1. Paracrine overproduction of ET-1, 5-HT, angiotensin II, and FGF-2 contributes to an increased pulmonary vascular cell proliferation, survival, migration, and differentiation. Many of these abnormalities both elevate vascular tone and promote endothelial and smooth muscle cell proliferation followed by structural changes or remodeling of the pulmonary vascular bed, which in turn results in an increase in pulmonary vascular resistance. In addition, in the adventitia there is increased production of extracellular matrix including collagen, elastin, fibronectin, and tenascin.

[0014] Over the past two decades, three main mechanistic pathways, namely the endothelin, nitric oxide and prostacyclin (prostaglandin (PG) I₂) pathways are targeted for PAH-specific therapies. The PAH-specific drug classes include the endothelin receptor antagonists, phosphodiesterase type-5 inhibitors (PDE-5i), including bosentan, sitaxsentan and ambrisentan and others such as sildenafil, tadalafil, or soluble guanylate cyclase stimulators and prostanoids. These “targeted” therapies have led to both short- and long-term benefits to many patients. All of the currently approved PAH drugs belong to one of these classes. These agents have received their initial regulatory approval as monotherapy for the primary indication by improving six-minute walk distance (6MWD). Additional endpoints such as functional class, hemodynamics, and clinical worsening of PAH have also been included in most of these Phase III trials. In these registration trials, drugs in these classes have been universally shown to improve exercise capacity and haemodynamics of patients with PAH. In addition, some of these drugs were shown to be associated with improvements in outcome for patients with PAH compared with historical data.

[0015] All of the currently approved PAH drugs belong to one of these classes, including, prostenoids, for example, epoprostenol (Flolan® and Veletri® intravenous infusions), treprostinil (Remodulin® subcutaneous/IV infusion); Tyvaso® (inhaled X4 time/day), Iloprost® (inhaled 6-9 times/day). These agents have received their initial regulatory approval as

monotherapy for the primary indication by improving six-minute walk distance (6MWD). Additional endpoints such as functional class, hemodynamics, and clinical worsening of PAH have also been included in most of these Phase III trials. In these registration trials, drugs in these classes have been universally shown to improve exercise capacity and haemodynamics of patients with PAH. In addition, some of these drugs were shown to be associated with improvements in outcome for patients with PAH compared with historical data.

[0016] Parenteral prostacyclin analogs have been the most widely studied. Intravenous epoprostenol was the first US Food and Drug Administration (FDA)-approved treatment for PAH (approved in 1995). However, due to its extremely short half-life (3-5 min), epoprostenol needs to be delivered as a continuous intravenous infusion through an indwelling catheter, with the risk of rebound PAH and acute right heart failure in case of infusion interruption. Furthermore, due to the inherent chemical instability of epoprostenol at room temperature and neutral pH (room temperature stability <8 hours), ice packs are needed to slow decomposition throughout the infusion period. A thermostable epoprostenol preparation for infusion (Veletri®), which does not require cooling, has been approved for use by the FDA. However, serious adverse events related to the delivery system include pump malfunction, local site infection, catheter obstruction, and sepsis continues to be a barrier for its use.

[0017] Treprostinil, is a longer-acting tricyclic benzidine analogue of epoprostenol with a terminal elimination half-life of approximately 2 to 4 hours and a distribution half-life of approximately 40 minutes. Unlike epoprostenol, Treprostinil is chemically stable at room temperature allowing it to be administered at ambient temperature and overcomes some of the limitations associated with epoprostenol therapy. Treprostinil causes vasodilation of pulmonary and systemic arterial vascular beds, and inhibits platelet aggregation by binding to prostacyclin IP receptors located on the surface of vascular smooth muscle cells and platelets. Treprostinil (Remodulin®) was first approved by the FDA in 2002 for adults with WHO group I PAH and functional class II to class IV status for continuous subcutaneous infusion and is marketed by United Therapeutics (Silver Spring, MD). In a pivotal 12 week randomized, controlled trial of 470 patients, subcutaneous Treprostinil significantly improved exercise capacity compared with placebo. The most common adverse events noted in subcutaneous infusion of Treprostinil-treated patients were infusion site pain.

[0018] Currently, an oral, extended release tablet of treprostinil diolamine (Orenitran®) is also available. However, with orally delivered medications, the absorption of treprostinil may be inconsistent particularly taken with food. The pharmacological and physiochemical

properties of treprostinil make this drug amenable to intermittent administration via the inhaled route. Tyvaso® and Iloprost (Ventavis®) are solutions for inhalation, which need to be administered using a special nebulizer for a prolonged period of time and often times in a physician's office. Using Tyvaso® inhalation system [Opti- Neb ultrasonic nebulizer (NebuTec, Elsenfeld, Germany)]. The inhalation system is complex to assemble and use, cumbersome to administer the dose (patient need to reset the device 3 times during a treatment session after every 3 breaths) and was found to have high error rates in human factor study. There is a distinct risk of under dosing as patient need to take 9 breaths within a specified 90 second time limit. Additionally, breath counter mechanism is triggered by time (time related) and not by inspiration or expiration flow or effort (breath related) and thus patient can overdose or under dose themselves by taking more or less than prescribed breaths (dose) in the 90 seconds time limit. The system also requires 4 different cleaning schedule (daily, weekly, monthly and yearly). Accordingly, new methods of PAH treatment are needed to facilitate the administration of these products to a patient.

[0019] Drug delivery to lung tissue has been achieved using a variety of devices for inhalation, including, nebulizers and inhalers, such as metered dose inhalers and dry powder inhalers to treat local disease or disorders. Dry powder inhalers used to deliver medicaments to the lungs contain a dose system of a powder formulation usually either in bulk supply or quantified into individual doses stored in unit dose compartments such as hard gelatin capsules or blister packs. Bulk containers are equipped with a measuring system operated by the patient in order to isolate a single dose from the powder immediately before inhalation.

[0020] Dosing reproducibility with inhalers requires that the drug formulation is uniform and that the dose be delivered to a subject with consistency and reproducible results. Therefore, the dosing system ideally should operate to completely discharge all of the formulation effectively during an inspiratory maneuver when the patient is taking his/her dose. However, complete powder discharge from the inhaler is not required as long as reproducible dosing can be achieved. Flow properties of the powder formulation, and long term physical and mechanical stability in this respect, are more critical for bulk containers than they are for single unit dose compartments. Good moisture protection for preventing product degradation can be achieved more easily for unit dose compartments such as blisters. However, the materials used to manufacture the blisters allow air into the drug compartment and subsequently, the formulation loses viability with prolonged storage, particularly if the formulation to be delivered is hygroscopic. The ambient air permeating through the blisters carries in humidity that

destabilizes the active ingredient. Additionally, dry powder inhalers which use blisters to deliver a medicament by inhalation can suffer with inconsistency of dose delivery to the lungs due to variations in geometry of the air conduit architecture resulting from puncturing films or peeling films of the blisters.

[0021] Dry powder inhalers such as those described in U.S. Patents No. 7,305,986, 7,464,706, 8,499,757 and 8,636,001, which disclosures are incorporated herein by reference in their entirety, can generate primary drug particles, or suitable inhalation plumes during an inspiratory maneuver by deagglomerating the powder formulation within a capsule or cartridge comprising a single dose. The amount of fine powder discharged from the inhaler's mouthpiece during inhalation is largely dependent on, for example, the inter-particulate forces in the powder formulation and the efficiency of the inhaler to separate those particles so that they are suitable for inhalation. The benefits of delivering drugs via the pulmonary circulation are numerous and include rapid entry into the arterial circulation, avoidance of drug degradation by liver metabolism, and ease of use without discomfort.

[0022] Some dry powder inhaler products developed for pulmonary delivery have met with some success to date. However, due to lack of practicality and/or cost of manufacture, there is room for improvement. Some of the persistent problems observed with prior art inhalers, include lack of device ruggedness, inconsistency in dosing, inconvenience of the equipment, poor deagglomeration, problems with delivery in light of divorce from propellant use, high manufacturing costs, and/or lack of patient compliance. Therefore, the inventors have identified the need to design and manufacture new formulations and inhalers with consistent improved powder delivery properties, easy to use, and having discrete configurations which would allow for better patient compliance.

SUMMARY

[0023] The present disclosure is directed to compositions and methods for using the compositions in the treatment of pulmonary hypertension. In embodiments herewith, a composition is provided in a dry powder inhaler comprising a replaceable cartridge comprising a dry powder for inhalation for delivery to the lungs for local or systemic delivery into the pulmonary circulation. The dry powder inhaler is a breath-powered inhaler which is compact, reusable or disposable, has various shapes and sizes, and comprises a system of airflow conduit pathways for the effective and rapid delivery of powder medicament to the lungs and the systemic circulation.

[0024] In a particular embodiment, the method of treating pulmonary arterial hypertension utilizes a drug delivery system which is designed for drug delivery to the lungs, including by inhalation, for rapid delivery and onset of action of the active agent being delivered to target tissues using the arterial circulation in the lungs. In this method, the active agent can reach its target site in a therapeutically effective manner.

[0025] In one embodiment, the method comprises administering a stable pharmaceutical composition comprising, one or more active agents, including, a vasodilator, including, sildenafil, tadalafil, vardenafil, a prostaglandin or an analog thereof, for example, treprostinil or a pharmaceutically acceptable salt thereof, including treprostinil sodium, for treating PAH and delivering the treprostinil into the systemic circulation of a subject by pulmonary inhalation using a dry powder inhaler. In one embodiment, the method comprises providing to a patient in need of treatment a dry powder inhaler comprising treprostinil in a stable dry powder formulation, and administering the active agent by oral inhalation.

[0026] In one embodiment, the drug delivery system comprises a dry powder inhaler comprising a diketopiperazine-based drug formulation for delivering small molecules, for example, a prostaglandin, or analogs thereof including, tresprostinil and protein-based products for treating PAH. The method provides advantages over typical methods of drug delivery, such as, oral tablet and subcutaneous and intravenous injectable/infusion drug products that are sensitive to degradation and/or enzymatic deactivation.

[0027] In certain embodiments disclosed herein, a method for providing a prostaglandin formulation to a patient in need thereof is disclosed, the method comprising, selecting a patient to be treated for PAH patient, and administering to the patient a dry powder formulation comprising treprostinil; wherein the treprostinil is combined with a diketopiperazine to produce a pharmaceutical formulation or composition suitable for pulmonary inhalation, and delivering the treprostinil formulation using a breath-powered dry powder inhaler. In this and other embodiments, the dry powder formulations is provided in a reconfigurable cartridge comprising from about 1 μg to about 200 μg of treprostinil in the dry powder formulation per dose. In certain embodiments, the dry powder formulation can comprise from about 10 μg to about 300 μg of treprostinil per dose in a cartridge or capsule. In one embodiment, a cartridge for single use can comprise from about 10 μg to about 90 μg of treprostinil for at least one inhalation. In some embodiments, the dry powder formulation is delivered using at least one inhalation per use. In this and other embodiments, the dry powder formulation is delivered to a patient in less than 10 seconds, or less than 8 seconds or less than 6 seconds per inhalation or

breath. In one embodiment, the pharmaceutical dry powder composition comprises microcrystalline particles of fumaryl diketopiperazine wherein the particles have a specific surface area ranging from about 59 m²/g to about 63 m²/g and have a pore size ranging from about 23 nm to about 30 nm.

[0028] Also disclosed herein is a method of treating a pulmonary arterial hypertension disease or disorder comprising, selecting a patient to be treated with pulmonary arterial hypertension, or a patient with PAH which exhibits a condition treatable with an active agent, including treprostinil, epoprostenol, bosentan, ambrisentan, macisentan, sildenafil, tadalafil, riociguat and the like, or combinations thereof, which patients are typically treated only by oral or injectable administration; replacing the aforementioned therapy with an inhalation therapy comprising providing the patient with an inhaler comprising the active agent in a stable dry powder composition for treating the disease or disorder; wherein the stable dry powder composition comprises the active agent and a diketopiperazine; and administering the stable dry powder composition to the patient by pulmonary inhalation; thereby treating the disease or condition.

[0029] In an exemplary embodiment, the formulation for treating pulmonary arterial hypertension comprises treprostinil in an amount up to 200 µg per dose, for example, amounts of 1 µg, 5 µg, 10 µg, 15 µg, 20 µg, 30 µg, 60 µg, 90 µg, 100 µg, 120 µg, 150 µg, 180 µg, or 200 µg, and one or more pharmaceutically acceptable carriers and/or excipients per dose are to be administered to a subject. In this embodiment, the pharmaceutically acceptable carrier and/or excipient can be formulated for oral inhalation and can form particles, for example, a diketopiperazine, including, fumaryl diketopiperazine, sugars such as mannitol, xylitol, sorbitol, and trehalose; amino acids, including, glycine, leucine, isoleucine, methionine; surfactants, including, polysorbate 80; cationic salts, including, monovalent, divalent and trivalent salts, including, sodium chloride, potassium chloride, magnesium chloride, and zinc chloride; buffers such as citrates and tartrates, or combination of one or more carriers and/or excipients and the like. In a particular embodiment, the formulation comprises a dry powder comprising treprostinil, a sugar and an amino acid, wherein the sugar is mannitol or trehalose; and the amino acid is leucine or isoleucine and a cationic salt. In certain embodiments, the formulation can further comprise sodium chloride, potassium chloride, magnesium chloride or zinc chloride, sodium citrate, sodium tartrate, or combinations thereof.

[0030] In an exemplary embodiment, the treprostinil dose is administered using a dry powder inhaler for oral inhalation. In this embodiment, a treprostinil inhalation powder dose is

provided to a patient suffering with pulmonary arterial hypertension and in need of treatment; wherein the a dry powder inhaler comprises a container including, a cartridge, and the container or cartridge comprises the dry powder comprising treprostinil is administered in multiple daily doses for a period of six months and the treprostinil is administered by oral inhalation at an earlier time in the course of the disease to patients with Functional Class II as a first line monotherapy.

[0031] In one embodiment, a method for treating pulmonary arterial hypertension is provided comprising providing a patient in need of treatment a monotherapy using an inhalable dry powder comprising treprostinil and a pharmaceutically acceptable carrier, and/or excipient by oral inhalation using a dry powder inhaler and a container comprising the inhalable dry powder and administering the dry powder formulation to the patient. In some embodiments, the treprostinil formulation comprises fumaryl diketopiperazine particles.

[0032] In one embodiment, a method for treating pulmonary arterial hypertension is provided comprising providing a patient in need of treatment a combination therapy using an inhalable dry powder comprising treprostinil and fumaryl diketopiperazine, and administering separately in combination with orally administered drugs selected from prostacyclin analogues, endothelin receptor antagonists (ERAs), including bosentan, ambrisentan and macitentan, soluble guanine cyclase agonists/stimulators such as riociguat, and PDE-5 inhibitors, including sildenafil, vardenafil and tadalafil.

[0033] In another embodiment, a dry powder comprising treprostinil and fumaryl diketopiperazine can also be administered as a part of up-front combination therapy with an oral agent. In an alternate embodiment, an inhalable treprostinil composition comprising a dose of fumaryl diketopiperazine and treprostinil powder, wherein treprostinil is in an amount from about 1 μg to about 200 μg administered in combination with an oral agent such as a PDE-5 inhibitor, or an endothelin receptor antagonist and/or the combination therapy may also be administered to replace continuously parenteral infusion of prostacyclin analogs in patients with severe disease and classified in WHO Functional class IV. Phosphodiesterase inhibitors, including PDE-5 inhibitors can also be formulated for inhalation alone, or in combination with the treprostinil and can be administered subsequently if administered alone, as a combination therapy.

[0034] In another embodiment, the inhalation system comprises a breath-powered dry powder inhaler, a container or cartridge containing a dry powder, for delivering an active agent to the pulmonary tract and lungs, including a medicament, wherein the medicament can comprise,

for example, an inhalable drug formulation for pulmonary delivery such as a composition comprising a diketopiperazine in a crystalline powder form that self-assembles in a suspension, an amorphous powder form, and/or a microcrystalline powder form comprising crystallites that do not self-assemble in suspension, or combinations thereof, and an active agent, including, treprostinil, sildenafil, vardenafil, tadalafil, or combinations thereof.

[0035] In alternate embodiments, the dry powder for inhalation may be formulated with other carriers and/or excipients other than diketopiperazines, for example a sugar, including trehalose; buffers, including sodium citrate; salts, including, sodium chloride and zinc chloride, and one or more active agents, including, treprostinil, vardenafil, and sildenafil.

[0036] In embodiments herewith, the method of treating PAH comprises, administering to a patient with moderate to severe PAH a dry powder formulation comprising treprostinil and a pharmaceutically acceptable carrier and/or excipient in an amount up to 200 µg of treprostinil using a dry powder inhaler comprising a movable member for loading a container comprising the pharmaceutical composition and the movable member can configure a container to attain a dosing configuration from a container loading configuration so that inhaler creates an airflow through the inhaler during an inhalation maneuver to allow the contents of the container to enter the airflow path and greater than 60% of a dry powder dose in the container is delivered to the lungs in a single inhalation.

[0037] In some embodiments, the treatment regimen with an inhalation dry powder depends on the patient's need and can be one inhalation to replace each of a nebulization session performed with standard therapy, including, at least one to four inhalations per day depending on the severity of disease.

DETAILED DESCRIPTION

[0038] In embodiments disclosed herein, dry powder compositions and dry powder inhalers comprising a container or a cartridge for delivering dry powders including pharmaceutical medicaments to a subject by oral inhalation are described. In one embodiment, the dry powder inhaler is a breath-powered, dry powder inhaler, and the container or cartridge is designed to contain an inhalable dry powder, including but not limited to pharmaceutical formulations comprising an active ingredient, including a pharmaceutically active substance, and optionally, a pharmaceutically acceptable carrier. In particular, the dry powder inhalers are for the treatment of pulmonary arterial hypertension.

[0039] The dry powder inhalers are provided in various embodiments of shapes and sizes, and can be reusable, easy to use, inexpensive to manufacture and/or produced in high volumes in simple steps using plastics or other acceptable materials. Various embodiments of the dry powder inhalers are provided herein and in general, the inhalation systems comprise inhalers, powder-filled cartridges, and empty cartridges. The present inhalation systems can be designed to be used with any type of dry powder. In one embodiment, the dry powder is a relatively cohesive powder which requires optimal deagglomeration conditions. In one embodiment, the inhalation system provides a re-useable, miniature breath-powered inhaler in combination with single-use cartridges containing pre-metered doses of a dry powder formulation. The inhaler can deliver a dry powder dose in a single inhalation to a patient in treating pulmonary arterial hypertension in less than 10 seconds. In particular embodiments, oral inhalation can deliver greater than 60% of a powder dose in less than 6 seconds, in less than 4 seconds and in less than 2 seconds.

[0040] As used herein the term “a unit dose inhaler” refers to an inhaler that is adapted to receive a single enclosure, cartridge or container comprising a dry powder formulation and delivers a single dose of a dry powder formulation by inhalation from a single container to a user. It should be understood that in some instances multiple unit doses will be required to provide a user with a specified dosage.

[0041] As used herein a “cartridge” is an enclosure configured to hold or contain a dry powder formulation, a powder containing enclosure, which has a cup or container and a lid. The cartridge is made of rigid materials, and the cup or container is moveable relative to the lid in a translational motion or vice versa.

[0042] As used herein a “powder mass” is referred to an agglomeration of powder particles or agglomerate having irregular geometries such as width, diameter, and length.

[0043] As used herein a “unit dose” refers to a pre-metered dry powder formulation for inhalation. Alternatively, a unit dose can be a single enclosure including a container having a single dose or multiple doses of formulation that can be delivered by inhalation as metered single amounts. A unit dose enclosure/cartridge/container contains a single dose. Alternatively it can comprise multiple individually accessible compartments, each containing a unit dose.

[0044] As used herein, the term "about" is used to indicate that a value includes the standard deviation of error for the device or method being employed to determine the value.

[0045] As used herein, the term "microparticle" refers to a particle with a diameter of about 0.5 to about 1000 μm , irrespective of the precise exterior or interior structure. Microparticles having a diameter of between about 0.5 and about 10 microns can reach the lungs, successfully passing most of the natural barriers. A diameter of less than about 10 microns is required to navigate the turn of the throat and a diameter of about 0.5 μm or greater is required to avoid being exhaled. To reach the deep lung (or alveolar region) where most efficient absorption is believed to occur, it is preferred to maximize the proportion of particles contained in the "respirable fraction" (RF), generally accepted to be those particles with an aerodynamic diameter of about 0.5 to about 6 μm , though some references use somewhat different ranges, as measured using standard techniques, for example, with an Anderson Cascade Impactor. Other impactors can be used to measure aerodynamic particle size such as the NEXT GENERATION IMPACTOR™ (NGI™, MSP Corporation), for which the respirable fraction is defined by similar aerodynamic size, for example $< 6.4 \mu\text{m}$. In some embodiments, a laser diffraction apparatus is used to determine particle size, for example, the laser diffraction apparatus disclosed in U.S. Patents No. 8,508,732, which disclosure is incorporated herein in its entirety for its relevant teachings related to laser diffraction, wherein the volumetric median geometric diameter (VMGD) of the particles is measured to assess performance of the inhalation system. For example, in various embodiments cartridge emptying of $\geq 80\%$, 85% , or 90% and a VMGD of the emitted particles of $< 12.5 \mu\text{m}$, $< 7.0 \mu\text{m}$, or $< 4.8 \mu\text{m}$ can indicate progressively better aerodynamic performance.

[0046] Respirable fraction on fill (RF/fill) represents the percentage (%) of powder in a dose that is emitted from an inhaler upon discharge of the powder content filled for use as the dose, and that is suitable for respiration, i.e., the percent of particles from the filled dose that are emitted with sizes suitable for pulmonary delivery, which is a measure of microparticle aerodynamic performance. As described herein, a RF/fill value of 40% or greater than 40% reflects acceptable aerodynamic performance characteristics. In certain embodiments disclosed herein, the respirable fraction on fill can be greater than 50% . In an exemplary embodiment, a respirable fraction on fill can be up to about 80% , wherein about 80% of the fill is emitted with particle sizes $< 5.8 \mu\text{m}$ as measured using standard techniques.

[0047] As used herein, the term "dry powder" refers to a fine particulate composition that is not suspended or dissolved in a propellant, or other liquid. It is not meant to necessarily imply a complete absence of all water molecules.

[0048] As used herein, "amorphous powder" refers to dry powders lacking a definite repeating form, shape, or structure, including all non-crystalline powders.

[0049] The present disclosure also provides improved powders comprising microcrystalline particles, compositions, methods of making the particles, and therapeutic methods that allow for improved delivery of drugs to the lungs for treating diseases and disorders in a subject. Embodiments disclosed herein achieve improved delivery by providing crystalline diketopiperazine compositions comprising microcrystalline diketopiperazine particles having high capacity for drug adsorption yielding powders having high drug content of one or more active agents. Powders made with the present microcrystalline particles can deliver increased drug content in lesser amounts of powder dose, which can facilitate drug delivery to a patient. The powders can be made by various methods including, methods utilizing surfactant-free solutions or solutions comprising surfactants depending on the starting materials.

[0050] In alternate embodiments disclosed herein, the drug delivery system can comprise a dry powder for inhalation comprising a plurality of substantially uniform, microcrystalline particles, wherein the microcrystalline particles can have a substantially hollow spherical structure and comprise a shell which can be porous comprising crystallites of a diketopiperazine that do not self-assemble in a suspension or in solution. In certain embodiments, the microcrystalline particles can be substantially hollow spherical and substantially solid particles comprising crystallites of the diketopiperazine depending on the drug and/or drug content provided and other factors in the process of making the powders. In one embodiment, the microcrystalline particles comprise particles that are relatively porous, having average pore volumes of about $0.43 \text{ cm}^3/\text{g}$, ranging from about $0.4 \text{ cm}^3/\text{g}$ to about $0.45 \text{ cm}^3/\text{g}$, and average pore size ranging from about 23 nm to about 30 nm, or from about 23.8 nm to 26.2 nm as determined by BJH adsorption.

[0051] Certain embodiments disclosed herein comprise dry powders comprising a plurality of substantially uniform, microcrystalline particles, wherein the particles have a substantially spherical structure comprising a shell which can be porous, and the particles comprise crystallites of a diketopiperazine that do not self-assemble in suspension or solution, and have a volumetric median geometric diameter less than $5 \text{ }\mu\text{m}$; or less than $2.5 \text{ }\mu\text{m}$ and comprise an active agent.

[0052] In a particular embodiment herein, up to about 92% of the microcrystalline particles have a volumetric median geometric diameter of $5.8 \text{ }\mu\text{m}$. In one embodiment, the particle's shell is constructed from interlocking diketopiperazine microcrystals having one or more drugs

adsorbed on their surfaces. In some embodiments, the particles can entrap the drug in their interior void volume and/or combinations of the drug adsorbed to the crystallites' surface and drug entrapped in the interior void volume of the spheres.

[0053] In certain embodiments, a diketopiperazine composition comprising a plurality of substantially uniformly formed, microcrystalline particles is provided, wherein the particles have a substantially hollow spherical structure and comprise a shell comprising crystallites of a diketopiperazine that do not self-assemble; wherein the particles are formed by a method comprising the step of combining diketopiperazine having a trans isomer content ranging from about 45% to 65% in a solution and a solution of acetic acid without the presence of a surfactant and concurrently homogenizing in a high shear mixer at high pressures of up to 2,000 psi to form a precipitate; washing the precipitate in suspension with deionized water; concentrating the suspension and drying the suspension in a spray drying apparatus. The microcrystalline particles can be pre-formed without for later used, or combined with an active agent in suspension prior to spray drying.

[0054] The method can further comprise the steps of adding with mixing a solution comprising an active agent or an active ingredient such as a drug or bioactive agent along with other pharmaceutically acceptable carriers and/or excipients prior to the spray drying step so that the active agent or active ingredient is adsorbed and/or entrapped on or within the particles. Particles made by this process can be in the submicron size range prior to spray-drying.

[0055] In certain embodiments, a diketopiperazine composition comprising a plurality of substantially uniformly formed, microcrystalline particles is provided, wherein the particles have a substantially hollow spherical structure and comprise a shell comprising crystallites of a diketopiperazine that do not self-assemble, and the particles have a volumetric mean geometric diameter less than equal to 5 μm ; wherein the particles are formed by a method comprising the step of combining diketopiperazine in a solution and a solution of acetic acid without the presence of a surfactant and concurrently homogenizing in a high shear mixer at high pressures of up to 2,000 psi to form a precipitate; washing the precipitate in suspension with deionized water; concentrating the suspension and drying the suspension in a spray drying apparatus.

[0056] The method can further comprise the steps of adding with mixing a solution comprising an active agent or an active ingredient such as a drug or bioactive agent prior to the spray drying step so that the active agent or active ingredient is adsorbed and/or entrapped on

or within the particles. Particles made by this process can be in the submicron size range prior to spray-drying.

[0057] In certain embodiments, a diketopiperazine composition comprising a plurality of substantially uniformly formed, microcrystalline particles is provided, wherein the microcrystalline particles have a substantially hollow spherical structure and comprise a shell comprising crystallites of a diketopiperazine that do not self-assemble, and the particles have a volumetric mean geometric diameter less than equal to 5 μm ; wherein the particles are formed by a method comprising the step of combining diketopiperazine in a solution and a solution of acetic acid without the presence of a surfactant and without the presence of an active agent, and concurrently homogenizing in a high shear mixer at high pressures of up to 2,000 psi to form a precipitate; washing the precipitate in suspension with deionized water; concentrating the suspension and drying the suspension in a spray drying apparatus.

[0058] In certain embodiments wherein the starting material comprising the active ingredient is an extract exhibiting a high degree of viscosity, or a substance having a honey like viscous appearance, the microcrystalline particles are formed as above and by washing them in water using tangential flow filtration prior to combining with the extract or viscous material. After washing in water, the resultant particle suspension is lyophilized to remove the water and re-suspended in an alcohol solution, including ethanol or methanol prior to adding the active ingredient as a solid, or in a suspension, or in solution. In one embodiment, optionally, the method of making the composition comprises the step of adding any additional excipient, including one or more, amino acid, such as leucine, isoleucine, norleucine, methionine or one or more phospholipids, for example, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) or 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), concurrently with the active ingredient or subsequent to adding the active ingredient, and prior to spray drying. In certain embodiments, forming the composition comprises the step wherein the extract comprising desired active agents is optionally filtered or winterized to separate and remove layers of unwanted materials such as lipids to increase its solubility.

[0059] The method can further comprise the steps of adding a solution with mixing to the mixture, and wherein the mixing can optionally be performed with or without homogenization in a high shear mixer, wherein the solution comprises an active agent or an active ingredient such as a drug or bioactive agent prior to the spray drying step so that the active agent or active ingredient is adsorbed and/or entrapped within or on the surface of the particles. Particles made

by this process can be in the submicron size range prior to spray-drying, or the particles can be formed from the solution during spray-drying.

[0060] In some embodiments herewith, the drug content can be delivered on crystalline powders using FDKP and which are lyophilized or sprayed dried at contents to about 10%, or about 20%, or about 30% or higher. In embodiments using microcrystalline particles formed from FDKP, or FDKP disodium salt, and wherein the particles do not self-assemble and comprise submicron size particles, drug content can typically be greater than 0.01 % (w/w). In one embodiment, the drug content to be delivered with the microcrystalline particles of from about 0.01 % (w/w) to about 75 % (w/w); from about 1 % to about 50 % (w/w), from about 10 % (w/w) to about 25 % (w/w), or from about 10 % to about 20% (w/w), or from 5% to about 30%, or greater than 25% depending on the drug to be delivered. An example embodiment wherein the drug is a peptide such as insulin, the present microparticles typically comprise approximately 10 % to 45% (w/w), or from about 10 % to about 20% (w/w) insulin. In certain embodiments, the drug content of the particles can vary depending on the form and size of the drug to be delivered.

[0061] In an exemplary embodiment, the composition comprises a dry powder comprising microcrystalline particles of fumaryl diketopiperazine, wherein the treprostinil is adsorbed to the particles and wherein the content of the treprostinil in the composition comprises up to about 20% (w/w) and ranges from about 0.5% to about 10% (w/w), or from about 1% to about 5% (w/w) of the dry powder. In one embodiment, the composition herein can comprise other excipients suitable for inhalation such as amino acids including methionine, isoleucine and leucine. In this embodiment, the treprostinil composition can be used in the prevention and treatment of pulmonary hypertension by self-administering an effective dose comprising about 1 mg to 15 mg of a dry powder composition comprising microcrystalline particles of fumaryl diketopiperazine and treprostinil in a single inhalation. In a particular embodiment, the treprostinil content in the formulation can be from about 1 µg to about 200 µg. In one embodiment, the dry powder content of the cartridges comprising treprostinil can be 20 µg, 30 µg, 60 µg, 90 µg, 120 µg, 150 µg, 180 µg, or 200 µg.

[0062] In alternate embodiments, the pharmaceutically acceptable carrier for making dry powders can comprise any carriers or excipients useful for making dry powders and which are suitable for pulmonary delivery. Example of pharmaceutically suitable carriers and excipients include, sugars, including saccharides and polysaccharides, such as lactose, mannose, sucrose, mannitol, trehalose; citrates, amino acids such as glycine, L-leucine, isoleucine, trileucine,

tartrates, methionine, vitamin A, vitamin E, zinc citrate, sodium citrate, trisodium citrate, sodium tartrate, sodium chloride, zinc chloride, zinc tartrate, polyvinylpyrrolidone, polysorbate 80, phospholipids including diphosphotidylcholine and the like.

[0063] In one embodiment, a method of self-administering a dry powder formulation to one's lung(s) with a dry powder inhalation system is also provided. The method comprises: obtaining a dry powder inhaler in a closed position and having a mouthpiece; obtaining a cartridge comprising a pre-metered dose of a dry powder formulation in a containment configuration; opening the dry powder inhaler to install the cartridge; closing the inhaler to effectuate movement of the cartridge to a dose position; placing the mouthpiece in one's mouth, and inhaling once deeply to deliver the dry powder formulation.

[0064] In still yet a further embodiment, a method of treating obesity, hyperglycemia, insulin resistance, pulmonary hypertention, anaphylaxis, and/or diabetes is disclosed. The method comprises the administration of an inhalable dry powder composition or formulation comprising, for example, a diketopiperazine having the formula 2,5-diketo-3,6-di(4-X-aminobutyl)piperazine, wherein X is selected from the group consisting of succinyl, glutaryl, maleyl, and fumaryl. In this embodiment, the dry powder composition can comprise a diketopiperazine salt. In still yet another embodiment, there is provided a dry powder composition or formulation, wherein the diketopiperazine is 2,5-diketo-3,6-di-(4-fumaryl-aminobutyl)piperazine, with or without a pharmaceutically acceptable carrier, or excipient.

[0065] An inhalation system for delivering a dry powder formulation to a patient's lung(s) is provided, the system comprising a dry powder inhaler configured to have flow conduits with a total resistance to flow in a dosing configuration ranging in value from 0.065 to about 0.200 (\sqrt{kPa})/liter per minute. The dry powder inhaler can be provided comprising a dry powder formulation for single use that can be discarded after use, or with individual doses that are replaceable in a multiple use inhaler and the individual dose enclosures or containers can be discarded after use.

[0066] In one embodiment, a dry powder inhalation kit is provided comprising a dry powder inhaler as described above, one or more medicament cartridges comprising a dry powder formulation for treating a disorder or disease such as respiratory tract and lung disease, including pulmonary arterial hypertension, cystic fibrosis, respiratory infections, cancer, and other systemic diseases, including, endocrine disease, including, diabetes and obesity.

[0067] Methods of treating a disease or disorder in a patient with the dry powder inhaler embodiments disclosed herewith is also provided. The method of treatment comprises

providing to a patient in need of treatment a dry powder inhaler comprising a cartridge containing a dose of an inhalable formulation comprising an active ingredient selected from the group as described above and a pharmaceutical acceptable carrier and/or excipient; and having the patient inhale through the dry powder inhaler deeply for about 3 to 4 seconds to deliver the dose. In the method, the patient can resume normal breathing pattern thereafter.

[0068] The following examples illustrate some of the processes for making dry powders suitable for using with the inhalers described herein and data obtained from experiments using the dry powders.

Example 1

[0069] *Preparation of surfactant-free dry powder comprising FDKP microcrystalline powder for use with inhalers:* In an example embodiment, surfactant free dry-powders comprising FDKP microcrystalline particles were prepared. Using a dual-feed high shear mixer, approximately equal masses of acetic acid solution (Table 1) and FDKP solution (Table 2) held at about $25^{\circ}\text{C} \pm 5^{\circ}\text{C}$ were fed at 2000 psi through a 0.001-in² orifice to form a precipitate by homogenization. The precipitate was collected in deionized (DI) water of about equal temperature. The wt% content of FDKP microcrystallites in the suspension is about 2 – 3.5%. The suspension FDKP concentration can be assayed for solids content by an oven drying method. The FDKP microcrystallite suspension can be optionally washed by tangential flow filtration using deionized water. The FDKP microcrystallites can be optionally isolated by filtration, centrifugation, spray drying or lyophilization.

Table 1. Composition of Acetic Acid Solution

Component	Component Range (wt. %)
Acetic Acid	10.5 – 13.0
Deionized Water	87.0- 89.5

Table 2. Composition of FDKP Solution

Component	Component Range (wt. %)
FDKP	2.5 – 6.25
30% NH ₄ OH Solution	1.6 – 1.75
Deionized Water	92 – 95.9

[0070] Dry powders (A, B, C and D) comprising microcrystalline particles made by the methods described above were tested for various characteristics, including surface area, water content and porosity measurements. Four different powders were used in this experiments. All powders tested had a residual water content of 0.4%. Table 2a demonstrates data obtained from the experiments.

Table 2a	Surface Area	Pore Volume	Pore Size
Powder ID	BET Surface Area (m ² /g)	BJH Adsorption cumulative volume of pores (cm ³ /g)	BJH Adsorption average pore diameter (4V/A) (nm)
A	61.3	0.43	25.1
B	62.3	0.43	24.4
C	63.0	0.42	23.8
D	59.0	0.44	26.2

[0071] The data in Table 2a show that the surface area of sprayed-dried, bulk dry powder comprising the microcrystalline particles of the samples tested ranged from 59 m²/g to 63 m²/g. The porosity data indicate that the microcrystalline particles are relatively porous, having average pore volumes of about 0.43 cm³/g and average pore size ranging from about 23.8 nm to 26.2 nm as determined by BJH adsorption. The porosimetry data indicate that these particles differ from prior art FDKP microparticles which have been shown to have an average pore volume of about 0.36 cm³/g and average pore size from about 20 nm to about 22.6 nm.

Example 2

[0072] *Preparation of dry powder comprising microcrystalline FDKP particles containing treprostinil.* A solution containing 0.2 – 1.0 wt% treprostinil in ethyl alcohol was added to a suspension of FDKP microcrystallites obtained as described in Example 1. The mixture was spray dried using a Buchi B290 spray-dryer equipped with a high efficiency cyclone. Nitrogen was used as the process gas (60 mm). Mixture were dried using 10-12% pump capacity, 90-100% aspiration rate, and an inlet temperature of 170 – 190°C. The weight % concentration of treprostinil in the resultant powder was 0.5 – 10%. Delivery efficiencies of these powders after discharge from a dry powder inhaler ranged between approximately 50% and 70%.

Example 3

[0073] *Use of treprostinil-fumaryl diketopiperazine composition in healthy subjects.* This study was an open-label, single ascending dose study in 36 healthy normal volunteers that were sequentially assigned to 6 cohorts receiving single doses of TreT (30, 60, 90, 120, 150, and 180 µg). The safety and tolerability of the dry powder compositions comprising treprostinil

was evaluated in each sequential cohort prior to escalating the dose for the next cohort using a dry powder inhaler system comprising a cartridge dose in a single inhalation. Blood samples were obtained before administration of the composition and at selected times through 480 minutes post-dose. Blood samples were analyzed for treprostinil using a validated analytical method and PK parameters were calculated using non-compartmental methods.

[0074] A total of 36 individuals were randomized and dosed. There were no severe adverse events, serious adverse events, or deaths during this study. No adverse events led to a subject's early termination. The most frequently reported adverse events were cough (n=11, 30.6%) and headache (n=8, 22%). Bioanalysis data confirmed that the treprostinil plasma concentrations and exposure for treprostinil, achieved clinically relevant concentrations comparable to those observed in historical Tyvaso® single dose clinical studies. C_{max} and AUC for treprostinil, increased in a linear manner with increasing dose. Overall, treprostinil was safe and well-tolerated and produced clinically relevant concentrations of treprostinil when inhaled as a dry powder.

[0075] The preceding disclosures are illustrative embodiments. It should be appreciated by those of skill in the art that the devices, techniques and methods disclosed herein elucidate representative embodiments that function well in the practice of the present disclosure. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments that are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

[0076] Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as molecular weight, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques. Notwithstanding that the numerical ranges and parameters setting forth the broad scope are approximations, the numerical values set forth in the specific examples are reported as precisely as possible. Any numerical value, however, inherently contains certain errors necessarily resulting from the standard deviation found in their respective testing measurements.

[0077] The terms "a" and "an" and "the" and similar referents used in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. Recitation of ranges of values herein is merely intended to serve as a shorthand method of referring individually to each separate value falling within the range. Unless otherwise indicated herein, each individual value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g. "such as") provided herein is intended merely to better illuminate the invention and does not pose a limitation on the scope otherwise claimed. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the invention.

[0078] The use of the term "or" in the claims is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and "and/or."

[0079] Groupings of alternative elements or embodiments disclosed herein are not to be construed as limitations. Each group member may be referred to and claimed individually or in any combination with other members of the group or other elements found herein. It is anticipated that one or more members of a group may be included in, or deleted from, a group for reasons of convenience and/or patentability. When any such inclusion or deletion occurs, the specification is herein deemed to contain the group as modified thus fulfilling the written description of all Markush groups used in the appended claims.

[0080] Preferred embodiments are described herein, including the best mode known to the inventors for carrying out the invention. Of course, variations on those preferred embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventor expects those of ordinary skill in the art to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

[0081] Specific embodiments disclosed herein may be further limited in the claims using consisting of or consisting essentially of language. When used in the claims, whether as filed

or added per amendment, the transition term “consisting of” excludes any element, step, or ingredient not specified in the claims. The transition term “consisting essentially of” limits the scope of a claim to the specified materials or steps and those that do not materially affect the basic and novel characteristic(s). Embodiments so claimed are inherently or expressly described and enabled herein.

[0082] Furthermore, numerous references have been made to patents and printed publications throughout this specification. Each of the above cited references and printed publications are herein individually incorporated by reference in their entirety.

[0083] Further, it is to be understood that the embodiments disclosed herein are illustrative of the principles of the present invention. Other modifications that may be employed are within the scope of the invention. Thus, by way of example, but not of limitation, alternative configurations may be utilized in accordance with the teachings herein. Accordingly, the present invention is not limited to that precisely as shown and described.

We claim:

1. A pharmaceutical dry powder composition comprising a treprostiniol dose in an amount of up to 200 μg and one or more pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier and/or excipients.
2. The pharmaceutical dry powder composition of claim 1, wherein the one or more pharmaceutically acceptable carrier and/or excipient is a diketopiperazine.
3. The pharmaceutical dry powder composition of claim 2, wherein the diketopiperazine is fumaryl diketopiperazine and comprises microcrystalline particles comprising crystallites of the diketopiperazine and the treprostiniol.
4. The pharmaceutical dry powder composition of claim 1, wherein the treprostiniol is from about 1 μg to about 180 μg in the dry powder composition.
5. The pharmaceutical dry powder composition of claim 1, wherein the pharmaceutical dry powder composition is in substantially crystalline form.
6. The pharmaceutical dry powder composition of claim 1, wherein the one or more pharmaceutically acceptable carrier and/or excipients is selected from lactose, mannose, sucrose, mannitol, trehalose, sodium citrate, trisodium citrate, zinc citrate, glycine, L-leucine, isoleucine, trileucine, sodium tartrate, zinc tartrate, methionine, vitamin A, vitamin E, sodium chloride, zinc chloride, polyvinylpyrrolidone, or polysorbate 80.
7. The pharmaceutical dry powder composition of claim 6, wherein the one or more pharmaceutically acceptable carrier and/or excipient are sodium citrate, sodium chloride, leucine or isoleucine, and trehalose.

8. The pharmaceutical dry powder composition of claim 7, further comprising polysorbate 80.
9. The pharmaceutical dry powder composition of claim 3, wherein microcrystalline particles have a specific surface area ranging from about 59 m²/g to about 63 m²/g.
10. The pharmaceutical dry powder composition of claim 3, wherein microcrystalline particles have a pore size ranging from about 23 nm to about 30 nm.
11. A dry powder inhaler comprising a movable member to load an enclosure and configure the container to attain a dosing configuration, wherein said enclosure comprises the pharmaceutical dry powder composition of claim 1.
12. The dry powder inhaler of claim 11, wherein the enclosure comprises a cartridge consisting of a lid and a container.
13. A method of treating pulmonary arterial hypertension comprising administering to a patient in need of treatment by oral inhalation using a dry powder inhaler comprising a dry powder composition comprising up to 200 µg of treprostinil or a pharmaceutically acceptable salt thereof, and/or one or more pharmaceutically acceptable carrier and/or excipient.
14. The method of treating pulmonary arterial hypertension of claim 11, wherein the one or more pharmaceutically acceptable carrier and/or excipients is selected from the group consisting of fumaryl diketopiperazine, lactose, mannose, sucrose, mannitol, trehalose, sodium citrate, trisodium citrate, zinc citrate, glycine, L-leucine, isoleucine, trileucine, sodium tartrate, zinc tartrate, methionine, vitamin A, vitamin E, sodium chloride, zinc chloride, polyvinylpyrrolidone, and polysorbate 80.

15. The method of treating pulmonary arterial hypertension of claim 12, wherein the one or more pharmaceutically acceptable carrier and/or excipient are sodium citrate, sodium chloride, leucine or isoleucine, and trehalose.

16. The method of treating pulmonary arterial hypertension of claim 11, wherein the one or more pharmaceutically acceptable carrier and/or excipient is fumaryl dikepiperazine.

17. The method of treating pulmonary arterial hypertension of claim 11, wherein the dry powder composition is administered in at least one inhalation in less than 10 seconds.

18. A pharmaceutical dry powder composition for treatment of pulmonary arterial hypertension comprising orally administering via inhalation using a dry powder inhaler comprising a dry powder composition comprising up to 200 µg of treprostinil or a pharmaceutically acceptable salt thereof, and/or one or more pharmaceutically acceptable carrier and/or excipient.

19. The pharmaceutical dry powder composition of claim 18, wherein the one or more pharmaceutically acceptable carrier and/or excipients is selected from the group consisting of fumaryl diketopiperazine, lactose, mannose, sucrose, mannitol, trehalose, sodium citrate, trisodium citrate, zinc citrate, glycine, L-leucine, isoleucine, trileucine, sodium tartrate, zinc tartrate, methionine, vitamin A, vitamin E, sodium chloride, zinc chloride, polyvinylpyrrolidone, and polysorbate 80.

20. The pharmaceutical dry powder composition of claim 19, wherein the one or more pharmaceutically acceptable carrier and/or excipient are sodium citrate, sodium chloride, leucine or isoleucine, and trehalose.

21. The pharmaceutical dry powder composition of claim 18, wherein the one or more pharmaceutically acceptable carrier and/or excipient is fumaryl dikepiperazine.

22. The pharmaceutical dry powder composition of claim 18, wherein the dry powder composition is administered in at least one inhalation in less than 10 seconds.

23. An inhaler including a pharmaceutical dry powder composition for treatment of pulmonary arterial hypertension comprising orally administering a dry powder composition comprising up to 200 µg of treprostinil or a pharmaceutically acceptable salt thereof, and/or one or more pharmaceutically acceptable carrier and/or excipient.

24. The inhaler of claim 23, wherein the one or more pharmaceutically acceptable carrier and/or excipients is selected from the group consisting of fumaryl diketopiperazine, lactose, mannose, sucrose, mannitol, trehalose, sodium citrate, trisodium citrate, zinc citrate, glycine, L-leucine, isoleucine, trileucine, sodium tartrate, zinc tartrate, methionine, vitamin A, vitamin E, sodium chloride, zinc chloride, polyvinylpyrrolidone, and polysorbate 80.

25. The inhaler of claim 24, wherein the one or more pharmaceutically acceptable carrier and/or excipient are sodium citrate, sodium chloride, leucine or isoleucine, and trehalose.

26. The inhaler of claim 23, wherein the one or more pharmaceutically acceptable carrier and/or excipient is fumaryl dikepipiperazine.

27. The inhaler of claim 23, wherein the dry powder composition is administered in at least one inhalation in less than 10 seconds.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 1951300.00393WO	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US 19/36095	International filing date (day/month/year) 07 June 2019 (07.06.2019)	(Earliest) Priority Date (day/month/year) 07 June 2018 (07.06.2018)
Applicant MANKIND CORPORATION		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed.
☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

- ☒ the text is approved as submitted by the applicant.
☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant.
☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. _____
☐ as suggested by the applicant.
☐ as selected by this Authority, because the applicant failed to suggest a figure.
☐ as selected by this Authority, because this figure better characterizes the invention.
b. ☒ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 19/36095

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/557; A61K 9/00; A61K 9/48 (2019.01)
CPC - A61K 31/557; A61K 31/5575; A61K 9/0075; A61K 9/4858

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2017/0216538 A1 (MannKind Corporation) 03 August 2017 (03.08.2017); entire document, especially the Abstract, FIGS. 1-5 and paragraphs [0011], [0025], [0061], [0085], [0094], [0107], [0109], [0114], [0124] and [0125].	1-27
A	US 5,503,852 A (Steiner et al.) 02 April 1996 (02.04.1996); entire document.	1-27
A	US 7,799,344 B2 (Oberg, K.) 21 September 2010 (21.09.2010); entire document.	1-27
A	US 9,089,497 B2 (MannKind Corporation) 28 July 2015 (28.07.2015); entire document.	1-27
A	US 2016/0031833 A1 (MannKind Corporation) 04 February 2016 (04.02.2016); entire document.	1-27



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

07 August 2019

Date of mailing of the international search report

26 AUG 2019

Name and mailing address of the ISA/US

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Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

EXHIBIT 22

CONFIDENTIAL - FILED UNDER SEAL

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS
CORPORATION,

Plaintiff,

v.

LIQUIDIA TECHNOLOGIES, INC.,

Defendant.

C.A. No. 1:23-cv-00975-RGA

HIGHLY CONFIDENTIAL

**DEFENDANT LIQUIDIA TECHNOLOGIES, INC.'S
FIRST AMENDED INVALIDITY CONTENTIONS**

To the extent UTC argues the the Asserted Claims are not invalid under §§ 102 and/or 103, the Asserted Claims of the '327 patent are invalid under 35 U.S.C. § 112 for lack of written description support, lack of enablement, and indefiniteness.

A. The Asserted Claims of the '327 Patent Lack Adequate Written Description

“[T]he test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.” *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). An adequate written description need not in every instance describe an actual reduction to practice but “must nonetheless ‘describe the claimed subject matter in terms that establish that [the applicant] was in possession of the . . . claimed invention, including all of the elements and limitations.’” *University of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 926 (Fed. Cir. 2004) (quoting *Hyatt v. Boone*, 146 F.3d 1348, 1353 (Fed. Cir. 1998)).

1. The Limitation reciting “statistically significant . . . in the patient” is not adequately described

Asserted Claims 2, 4, 9, and 10 of the '327 patent, all dependent claims of Asserted Claim 1, and for Claim 10, dependent Claim 9, all require a “statistically significant [increase/reduction/improvement] ... in the patient.” A POSA would have understood the “the patient” limitation of Asserted Claims 2, 4, 9, and 10 as referencing back to the “a patient” limitation in Asserted Claim 1. As proposed by Liquidia, the terms “a” and “the” mean “one and more than one.” This construction is consistent with the specification of the '327 patent which states that “as used herein and in the appended claims, the singular forms ‘a,’ ‘an,’ and ‘the’ include plural referents unless the context clearly dictates otherwise.” ('327 patent at UTC_PH-ILD_005335 (6:15-17).) Thus, a POSA would have understood the “the patient” term in dependent Asserted Claims 2, 4, 9, and 10 include “one” patient. In other words, a POSA would

EXHIBIT 23

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Transcript of Richard Channick, M.D.

Date: April 6, 2024

Case: United Therapeutics Corporation -v- Liquidia Technologies, Inc.

Planet Depos

Phone: 888.433.3767

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www.planetdepos.com

Transcript of Richard Channick, M.D.

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Conducted on April 6, 2024

<p>1 UNITED STATES DISTRICT COURT</p> <p>2 FOR THE DISTRICT OF DELAWARE</p> <p>3</p> <p>4 UNITED THERAPEUTICS CORPORATION,)</p> <p>5 PLAINTIFF,)</p> <p>6)</p> <p>7 VS.) CASE NO.</p> <p>8) 23-975 (RGA)</p> <p>9 LIQUIDIA TECHNOLOGIES, INC.,)</p> <p>10 DEFENDANT.)</p> <p>11 -----</p> <p>12</p> <p>13</p> <p>14</p> <p>15 DEPOSITION</p> <p>16 DR. RICHARD CHANNICK</p> <p>17 SATURDAY, APRIL 6, 2024</p> <p>18 SANTA MONICA,, CALIFORNIA</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24 PAGES 1 - 194</p> <p>25 REPORTED BY MICHAEL CAGLIATA</p> <p>CSR #14491, RPR</p>	<p>1 A P P E A R A N C E S</p> <p>2</p> <p>3 For the Plaintiff:</p> <p>4 GOODWIN PROCTER, LLP</p> <p>5 BY: ADAM HOROWITZ, ESQ.</p> <p>6 BY: ERIC ROMEO, ESQ.</p> <p>7 THE NEW YORK TIMES BUILDING</p> <p>8 620 EIGHTH AVENUE</p> <p>9 NEW YORK, NEW YORK 10018</p> <p>10 212-813-8800</p> <p>11</p> <p>12 For the Defendant:</p> <p>13 COOLEY</p> <p>14 BY: SANYA SUKDUANG, ESQ.</p> <p>15 1299 PENNSYLVANIA AVENUE, NW. SUITE 700</p> <p>16 WASHINGTON, DC 20004-2400</p> <p>17 202-842-7800</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p>								
<p>1</p> <p>2 Deposition of</p> <p>3 DR. RICHARD CHANNICK, held in person:</p> <p>4</p> <p>5 Witness Location:</p> <p>6 COOLEY LLP (SANTA MONICA)</p> <p>7 1333 2ND STREET, SUITE 400</p> <p>8 SANTA MONICA, CA 90401</p> <p>9</p> <p>10</p> <p>11</p> <p>12 Pursuant to Notice, before Michael</p> <p>13 Cagliata, Registered Professional Reporter, and</p> <p>14 Certified Shorthand Reporter No. 14491 in and for the</p> <p>15 State of California.</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p>	<p>1 INDEX</p> <table><thead><tr><th data-bbox="878 1129 992 1148">WITNESS NAME</th><th data-bbox="1330 1129 1369 1148">PAGE</th></tr></thead><tbody><tr><td data-bbox="878 1161 1130 1180">DR. RICHARD CHANNICK, SWORN</td><td></td></tr><tr><td data-bbox="971 1192 1195 1211">EXAMINATION BY MR. ROMEO</td><td data-bbox="1354 1192 1369 1211">7</td></tr><tr><td data-bbox="971 1224 1222 1243">EXAMINATION BY MR. SUKDUANG</td><td data-bbox="1338 1224 1369 1243">185</td></tr></tbody></table> <p>2</p> <p>3</p> <p>4</p> <p>5</p> <p>6</p> <p>7</p> <p>8</p> <p>9</p> <p>10</p> <p>11</p> <p>12</p> <p>13</p> <p>14</p> <p>15</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p>	WITNESS NAME	PAGE	DR. RICHARD CHANNICK, SWORN		EXAMINATION BY MR. ROMEO	7	EXAMINATION BY MR. SUKDUANG	185
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<p>5</p> <p>1 EXHIBIT INDEX</p> <p>2 EXHIBIT NUMBER PAGE</p> <p>3 1 DECLARATION 12</p> <p>4 2 LETTER TO THE EDITOR 28</p> <p>5 3 TYVASO LABEL 37</p> <p>6 4 ARTICLE 42</p> <p>7 5 ARTICLE 48</p> <p>8 6 SCREENSHOT 52</p> <p>9 7 ARTICLE 61</p> <p>10 8 GUIDELINES 70</p> <p>11 9 TRANSCRIPT 83</p> <p>12 10 LIQUIDIA REBUTTAL HILL REPORT 87</p> <p>13 11 793 PATENT 93</p> <p>14 12 ARTICLE 98</p> <p>15 13 VIDEO TRANSCRIPT 105</p> <p>16 14 PATENT 114</p> <p>17 15 ARTICLE 130</p> <p>18 16 APPENDIX 130</p> <p>19 17 STUDY 133</p> <p>20 18 EARNINGS CALL TRANSCRIPT 141</p> <p>21 19 ABSTRACT 144</p> <p>22 20 ARTICLE 149</p> <p>23 21 ARTICLE 156</p> <p>24 22 PRESS RELEASE 160</p> <p>25 23 PROPOSED YUTREPIA LABEL 163</p>	<p>7</p> <p>1 MR. SUKDUANG: Sanya Sukduang from Cooley</p> <p>2 on behalf of Liquidia and Dr. Channick.</p> <p>3 VIDEOGRAPHER: Our court reporter today is</p> <p>4 Michael Cagliata representing Planet Depos. You may</p> <p>5 now swear in the witness.</p> <p>6 (Oath given.)</p> <p>7 EXAMINATION BY MR. ROMEO</p> <p>8 Q. Good morning, Dr. Channick.</p> <p>9 A. Good morning.</p> <p>10 Q. My name is Eric Romeo, I'm going to be</p> <p>11 taking your deposition today. Let's start with the</p> <p>12 easiest question. Can you please state your name for</p> <p>13 the record?</p> <p>14 A. Richard Channick.</p> <p>15 Q. What's your home address?</p> <p>16 A. Home address?</p> <p>17 Q. Yes.</p> <p>18 A. [REDACTED]</p> <p>19 Q. Are you employed, sir?</p> <p>20 A. Yes.</p> <p>21 Q. Where are you employed?</p> <p>22 A. UCLA.</p> <p>23 Q. And what's your title?</p> <p>24 A. Professor of medicine.</p> <p>25 Q. Now, have you been deposed before?</p>
<p>6</p> <p>1 PROCEEDINGS</p> <p>2 * * * *</p> <p>3 VIDEOGRAPHER: Here begins media number one</p> <p>4 at the video deposition of Dr. Richard Channick in</p> <p>5 the matter of United Therapeutics Corporation versus</p> <p>6 Liquidia Technologies Inc. This case is being heard</p> <p>7 in the United States court of appeals for the federal</p> <p>8 circuit --</p> <p>9 MR. SUKDUANG: I'm sorry. That's wrong.</p> <p>10 VIDEOGRAPHER: Okay. That's what I've got.</p> <p>11 Can you say what it's for?</p> <p>12 MR. SUKDUANG: United States District Court</p> <p>13 for the District of Delaware.</p> <p>14 VIDEOGRAPHER: Okay. Today's date is</p> <p>15 April 6th, 2024, and the time is 8:59 A.M. Pacific</p> <p>16 time. The videographer today is Kevin Johnson</p> <p>17 representing Planet Depos. This video deposition is</p> <p>18 taking place at 1333 2nd street. We're in Suite 400.</p> <p>19 Santa Monica, California 90401. Could counsel please</p> <p>20 identify yourself and state whom you represent,</p> <p>21 beginning with the questioning attorney?</p> <p>22 MR. ROMEO: Eric Romeo from Goodwin for</p> <p>23 plaintiff United Therapeutics. With me today is Adam</p> <p>24 Horowitz, also from Goodwin, as well as Adam</p> <p>25 Burrowbridge from McDermott Will and Emery.</p>	<p>8</p> <p>1 A. Yes.</p> <p>2 Q. Approximately how many times?</p> <p>3 A. More than 100.</p> <p>4 Q. More than 100. And what types of cases</p> <p>5 generally have you been involved in?</p> <p>6 A. Product liability cases and medical</p> <p>7 malpractice cases.</p> <p>8 Q. Okay. Have you been involved in any patent</p> <p>9 litigation cases like this one before?</p> <p>10 A. Not that I recall.</p> <p>11 Q. Okay. Do you remember serving as a witness</p> <p>12 in a case involving United Therapeutics and Watson?</p> <p>13 A. I don't recall that.</p> <p>14 Q. Okay. So to your memory, this is the first</p> <p>15 patent case in which you've served as an expert</p> <p>16 witness?</p> <p>17 A. I believe so.</p> <p>18 Q. Okay. So given that you've had the</p> <p>19 privilege of being deposed over 100 times, I'm not</p> <p>20 going to spend a lot of time on the ground rules for</p> <p>21 the deposition. As you know, the way this is going</p> <p>22 to go today is I'm going to ask you questions, you're</p> <p>23 going to answer the questions, your counsel may</p> <p>24 object from time to time, but unless he explicitly</p> <p>25 instructs you not to answer the question, you need to</p>

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<p>9</p> <p>1 answer my questions to the best of your ability. Do</p> <p>2 you understand that?</p> <p>3 A. Yes.</p> <p>4 Q. Okay. And because you're under oath here</p> <p>5 today, it's very important that you understand my</p> <p>6 questions. And so please, if you have any questions</p> <p>7 about my questions or you would like clarification,</p> <p>8 please feel free to ask me. You're not going to hurt</p> <p>9 my feelings. But I will assume that if you answered</p> <p>10 a question that I asked that you understood it. Is</p> <p>11 that fair?</p> <p>12 A. Yes.</p> <p>13 Q. Okay. Now, today we're going to take</p> <p>14 breaks. I generally like to take breaks about every</p> <p>15 hour but if you would like to go longer or shorter</p> <p>16 and you would like a break, please let me know. The</p> <p>17 only thing I ask is that before we leave on a break,</p> <p>18 if there's a question pending that you answer it</p> <p>19 before we go on break. Is that fair?</p> <p>20 A. Yes.</p> <p>21 Q. Okay. You understand today that you're</p> <p>22 testifying as if you were in court?</p> <p>23 A. Yes.</p> <p>24 Q. And you understand that this case as</p> <p>25 counsel pointed out is pending in the federal</p>	<p>11</p> <p>1 working on this case?</p> <p>2 A. 20.</p> <p>3 Q. Okay. Did you do anything to prepare for</p> <p>4 your deposition today?</p> <p>5 A. Yes.</p> <p>6 Q. What did you do? Again, I'm not looking</p> <p>7 for the substance of any privileged conversations?</p> <p>8 A. Reviewed my declaration, I had a meeting</p> <p>9 with the attorney to discuss my testimony in the</p> <p>10 case, and then reviewed some of the articles that are</p> <p>11 cited in the declaration.</p> <p>12 Q. Okay. You mentioned that you met with</p> <p>13 counsel. When did you meet with counsel?</p> <p>14 A. Last? I met with counsel several times.</p> <p>15 Q. Okay. In preparation for today's</p> <p>16 deposition?</p> <p>17 A. Yesterday.</p> <p>18 Q. Okay. And about how long did you meet with</p> <p>19 counsel yesterday?</p> <p>20 A. Five hours.</p> <p>21 Q. Okay. And who was present for that</p> <p>22 meeting?</p> <p>23 A. Just Sanya and myself.</p> <p>24 Q. Okay. You mentioned you reviewed</p> <p>25 documents. Do you recall approximately how many</p>
<p>10</p> <p>1 district court for the district of Delaware and that</p> <p>2 this deposition is being conducted according to the</p> <p>3 rules of that court?</p> <p>4 A. Yes.</p> <p>5 Q. And you understand that according to the</p> <p>6 rules of the district court for the district of</p> <p>7 Delaware that during breaks you're not to discuss the</p> <p>8 substance of your testimony with counsel. Do you</p> <p>9 understand that?</p> <p>10 A. I mean, I heard what you said. Yes. I</p> <p>11 don't know the law related to that.</p> <p>12 Q. Okay. Is there any reason that you would</p> <p>13 be unable to answer my questions truthfully and</p> <p>14 accurately today?</p> <p>15 A. No.</p> <p>16 Q. Okay. When were you first retained to work</p> <p>17 on this case, United Therapeutics versus Liquidia?</p> <p>18 A. Probably a few months ago. I couldn't give</p> <p>19 a more specific date. Probably three or four months</p> <p>20 or so.</p> <p>21 Q. Okay. Do you remember who contacted you?</p> <p>22 A. I believe it was Sanya Sukduang.</p> <p>23 MR. SUKDUANG: Sanya is fine.</p> <p>24 Q. We know who you're talking about. And as</p> <p>25 of today, approximately how many hours have you spent</p>	<p>12</p> <p>1 documents you reviewed in preparation for today's</p> <p>2 deposition?</p> <p>3 A. Ten.</p> <p>4 Q. Okay. And were all the documents that you</p> <p>5 reviewed in preparation for today's deposition</p> <p>6 documents that you relied on or considered in</p> <p>7 preparing your declaration in this case?</p> <p>8 A. Yes.</p> <p>9 Q. Okay. Dr. Channick, the court reporter's</p> <p>10 handed you what's been marked as Exhibit 1.</p> <p>11 (Exhibit 1 marked for identification.)</p> <p>12 Q. Do you recognize Exhibit 1?</p> <p>13 A. Yes.</p> <p>14 Q. What is Exhibit 1?</p> <p>15 A. That's my expert declaration.</p> <p>16 Q. And that's the expert declaration you</p> <p>17 submitted in this case; correct?</p> <p>18 A. I'd have to look through every page, but</p> <p>19 the first page is the same.</p> <p>20 Q. Okay. And if you could please turn to</p> <p>21 page 70 of the report -- of the declaration. I'm</p> <p>22 sorry. Is that your signature on page 70?</p> <p>23 A. Yes.</p> <p>24 Q. And you say here, "I declare under penalty</p> <p>25 of perjury the foregoing is true and correct." Do</p>

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<p>13</p> <p>1 you see that?</p> <p>2 A. Yes.</p> <p>3 Q. And the foregoing here refers to the</p> <p>4 content of the declaration that precedes it?</p> <p>5 A. Yes.</p> <p>6 Q. Okay. And the date there is March 30th,</p> <p>7 2024?</p> <p>8 A. Yes.</p> <p>9 Q. As of today, are there any corrections you</p> <p>10 would like to make to your declaration, Exhibit 1?</p> <p>11 A. No.</p> <p>12 Q. Okay. And then following your signature in</p> <p>13 Exhibit 1, there are two appendices; correct?</p> <p>14 A. Let me find the second one.</p> <p>15 Q. I believe Appendix A is only four pages.</p> <p>16 A. Okay. Then you're correct if that's the</p> <p>17 case. Yeah. Two.</p> <p>18 Q. Okay. And Appendix A is the materials you</p> <p>19 considered in preparing this declaration; is that</p> <p>20 correct?</p> <p>21 A. Yes.</p> <p>22 Q. And Appendix B is a copy of your CV last</p> <p>23 updated October 10, 2023; is that correct?</p> <p>24 A. Yes.</p> <p>25 Q. Okay. You told me earlier that you spent</p>	<p>15</p> <p>1 A. Yes.</p> <p>2 Q. Now, did you draft every word of this</p> <p>3 declaration?</p> <p>4 MR. SUKDUANG: Objection. Vague.</p> <p>5 THE WITNESS: What do you mean by "draft"?</p> <p>6 Q. Let me ask you a better question. Who</p> <p>7 drafted this declaration?</p> <p>8 MR. SUKDUANG: Objection. Vague.</p> <p>9 THE WITNESS: What do you mean by "draft"?</p> <p>10 Q. Do you see words written on the page in</p> <p>11 this declaration?</p> <p>12 A. Yes.</p> <p>13 Q. Who wrote those words?</p> <p>14 A. You mean who typed the words into a</p> <p>15 computer?</p> <p>16 Q. Yes.</p> <p>17 A. So as I presume you know, typically a</p> <p>18 declaration we have a discussion, based on my</p> <p>19 opinions and the discussions that we have with</p> <p>20 counsel, there's a draft given and the attorneys,</p> <p>21 presuming people in their office help draft it, write</p> <p>22 the first draft. I then go through it and edit it</p> <p>23 and make changes. The draft obviously reflects my</p> <p>24 opinion. And I type some of it, they type some of</p> <p>25 it, and we end up with this declaration.</p>
<p>14</p> <p>1 about 20 hours working on this case. Excluding the</p> <p>2 five hours you spent yesterday preparing for your</p> <p>3 deposition, approximately how many hours did you</p> <p>4 spend preparing your declaration, Exhibit 1?</p> <p>5 A. What do you mean by "preparing"?</p> <p>6 Q. Okay. You told me that you spent about</p> <p>7 20 hours on this case so far, and you told me that</p> <p>8 you spent five hours yesterday with counsel. Yes?</p> <p>9 A. Yes.</p> <p>10 Q. Okay. So if my math is correct that leaves</p> <p>11 about 15 hours. Of those 15 hours how many were</p> <p>12 devoted to assembling this document, Exhibit 1?</p> <p>13 A. I think you need to be more specific. What</p> <p>14 do you mean assembling? Discussing? Typing?</p> <p>15 Printing? All of the above?</p> <p>16 Q. Sure. Let's start all of the above and</p> <p>17 then we can take them one by one. So overall, how</p> <p>18 many hours did you spend preparing this document?</p> <p>19 A. 15.</p> <p>20 Q. 15. Okay. And in terms of actually</p> <p>21 writing or drafting the document, approximately how</p> <p>22 many hours did you spend?</p> <p>23 A. Three.</p> <p>24 Q. Okay. This declaration is approximately</p> <p>25 70 pages in length; is that correct?</p>	<p>16</p> <p>1 Q. Okay. You said, "you typed some of it".</p> <p>2 Which portions of Exhibit 1 did you yourself type?</p> <p>3 MR. SUKDUANG: Counsel, you understand</p> <p>4 under the district of Delaware drafts and forms of</p> <p>5 drafts are not permitted. So Dr. Channick, you can</p> <p>6 answer that generally.</p> <p>7 THE WITNESS: I mean, I don't recall which</p> <p>8 parts I drafted. I typed a lot of it. They typed a</p> <p>9 lot of it. I made changes and edits and corrections.</p> <p>10 So there's no way I could go through and tell you</p> <p>11 line by line which ones I typed. This is a very</p> <p>12 iterative process by which I made changes and</p> <p>13 corrections and wrote sections.</p> <p>14 Q. You mentioned "drafting". Approximately</p> <p>15 how many drafts, and again, I'm not looking for</p> <p>16 content. Approximately how many drafts were there of</p> <p>17 this declaration?</p> <p>18 A. Two or three.</p> <p>19 Q. Two or three. Let's turn to Appendix A,</p> <p>20 please. Appendix A is titled, "materials</p> <p>21 considered"; is that correct?</p> <p>22 A. Yes.</p> <p>23 Q. Is Appendix A a complete list of all the</p> <p>24 materials that you considered in preparing your</p> <p>25 declaration, Exhibit 1?</p>

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<p>17</p> <p>1 A. Yes, all of the written materials.</p> <p>2 Q. Are there any other materials that you</p> <p>3 considered in preparing Exhibit 1 other than those</p> <p>4 listed in Appendix A?</p> <p>5 A. No other written materials.</p> <p>6 Q. Were there any non-written materials that</p> <p>7 you considered in preparing your declaration?</p> <p>8 A. Yes.</p> <p>9 Q. What were those?</p> <p>10 A. My clinical experience in pulmonary</p> <p>11 hypertension.</p> <p>12 Q. Anything else?</p> <p>13 A. No.</p> <p>14 Q. Did you personally select each of the</p> <p>15 materials that are listed in Appendix A?</p> <p>16 MR. SUKDUANG: Objection. Vague.</p> <p>17 THE WITNESS: What do you mean by "select"?</p> <p>18 Q. You'll notice, doctor, that there are a</p> <p>19 number of bullet points listing written documents;</p> <p>20 correct?</p> <p>21 A. Yes.</p> <p>22 Q. And you reviewed each of these documents?</p> <p>23 A. Yes.</p> <p>24 Q. How did you come into possession of each of</p> <p>25 these documents?</p>	<p>19</p> <p>1 A. Yes.</p> <p>2 Q. Okay. Did you review those two materials</p> <p>3 in their entirety?</p> <p>4 A. Yes.</p> <p>5 Q. Do you see that the next nine bullets</p> <p>6 listed are litigation materials from other</p> <p>7 litigations involving United Therapeutics and</p> <p>8 Liquidia?</p> <p>9 A. Yes.</p> <p>10 Q. Were those provided to you by counsel?</p> <p>11 A. Yes.</p> <p>12 Q. Did you review every page of each of those</p> <p>13 other materials?</p> <p>14 A. I can't say with great confidence I</p> <p>15 reviewed every page, but I certainly reviewed them.</p> <p>16 Q. Do you know if these were the full copies</p> <p>17 of the documents or whether they were excerpted</p> <p>18 copies?</p> <p>19 A. I'm not aware.</p> <p>20 Q. Let's go to the other section. This is on</p> <p>21 page 4 of Appendix A. Do you see here that there is,</p> <p>22 about halfway down, a YouTube video from Dr. Nathan?</p> <p>23 A. Okay.</p> <p>24 Q. Do you remember if you selected this</p> <p>25 reference or if counsel did?</p>
<p>18</p> <p>1 A. Well, some of them are articles I've</p> <p>2 written. Some of them are articles that have been</p> <p>3 discussed with counsel and were provided to me to</p> <p>4 read because I didn't have them. Some of them are</p> <p>5 articles I pulled up myself on the Internet. I mean,</p> <p>6 you know, those are probably the ways that I came</p> <p>7 into possession of them.</p> <p>8 Q. Do you know, sitting here today, which of</p> <p>9 the documents listed in Exhibit A were provided to</p> <p>10 you by counsel?</p> <p>11 A. No.</p> <p>12 MR. SUKDUANG: Go ahead.</p> <p>13 THE WITNESS: No, I don't.</p> <p>14 Q. Do you know approximately how many of the</p> <p>15 materials listed in Appendix A you yourself</p> <p>16 retrieved, as you mentioned, from the Internet?</p> <p>17 MR. SUKDUANG: You can answer that</p> <p>18 generally.</p> <p>19 THE WITNESS: No, I don't.</p> <p>20 Q. Okay. Can you turn to the section</p> <p>21 entitled, "litigation materials", on page 3, please?</p> <p>22 A. Okay.</p> <p>23 Q. Do you see the first two entries here are</p> <p>24 relating to a declaration in deposition of Dr. Steven</p> <p>25 D. Nathan in this matter.</p>	<p>20</p> <p>1 A. I believe counsel did.</p> <p>2 Q. Did you watch the entirety of this video?</p> <p>3 A. No.</p> <p>4 Q. Which portions of this video did you watch?</p> <p>5 A. I think I just read the excerpt from it.</p> <p>6 Q. When you say "excerpt", what do you mean?</p> <p>7 A. This came from counsel, a quote from his</p> <p>8 talk at this summit.</p> <p>9 Q. So counsel provided you with particular</p> <p>10 quotes from the video; is that correct?</p> <p>11 A. I believe so.</p> <p>12 Q. Were you provided with a transcript of the</p> <p>13 video?</p> <p>14 A. I don't recall. I don't believe so.</p> <p>15 Q. Okay. But you haven't watched the video in</p> <p>16 its entirety?</p> <p>17 A. No.</p> <p>18 Q. Okay. Let's turn to Appendix B, please.</p> <p>19 What is Appendix B?</p> <p>20 A. My curriculum vitae.</p> <p>21 Q. And it was last updated October 10, 2023;</p> <p>22 is that correct?</p> <p>23 A. Yes.</p> <p>24 Q. Have you updated your CV since October of</p> <p>25 last year?</p>

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<p>21</p> <p>1 A. I don't believe so.</p> <p>2 Q. Okay.</p> <p>3 A. I need to do that.</p> <p>4 Q. We all do. Could you turn to the last page</p> <p>5 of your CV? I believe it's page 31.</p> <p>6 A. Okay.</p> <p>7 Q. I see that there's a signature here on the</p> <p>8 last page. Do you see that?</p> <p>9 A. Yes.</p> <p>10 Q. Is that your signature?</p> <p>11 A. Yes.</p> <p>12 Q. Is it customary for you to sign your CV?</p> <p>13 A. Oftentimes I do, yeah. If someone's asking</p> <p>14 for a CV, I often have a signature. That looks like</p> <p>15 an electronic signature that I applied probably a</p> <p>16 while ago.</p> <p>17 Q. Okay. And what's the signature at the end</p> <p>18 of the CV meant to indicate?</p> <p>19 A. It's my signature. I don't know.</p> <p>20 Q. Are you certifying to the correctness and</p> <p>21 completeness of the CV? Is that why you've signed</p> <p>22 it?</p> <p>23 A. Many times you're asked to sign your CV.</p> <p>24 If you're -- sometimes it has to be submitted for</p> <p>25 various things and they want it signed.</p>	<p>23</p> <p>1 called Connective Tissue Disease?</p> <p>2 A. Yes.</p> <p>3 Q. What is Connective Tissue Disease?</p> <p>4 A. Connective Tissue Disease is a broad group</p> <p>5 of, what we call autoimmune diseases, that affect</p> <p>6 various tissues, and there are a number of different</p> <p>7 connective tissue diseases. They're basically an</p> <p>8 autoimmune disease where the body develops antibodies</p> <p>9 to different parts of itself.</p> <p>10 Q. Of the 100 patients with PHILD that you</p> <p>11 treated over the last calendar year, approximately</p> <p>12 what percentage also have CTD or Connective Tissue</p> <p>13 Disease?</p> <p>14 A. Maybe 50 percent.</p> <p>15 Q. I'm sure we'll talk about this in more</p> <p>16 detail today, but how do you define a PHILD patient?</p> <p>17 What makes a PHILD a patient in your opinion?</p> <p>18 A. Not an easy question. First of all,</p> <p>19 because -- basically, the concept is with the</p> <p>20 classification system that we came up with 20 some</p> <p>21 years ago, is that there are different conditions</p> <p>22 that can cause pulmonary hypertension, pulmonary</p> <p>23 hypertension being high blood pressure in the lungs.</p> <p>24 One of those conditions is interstitial lung disease</p> <p>25 where the tissue between the alveoli and the blood</p>
<p>22</p> <p>1 Q. Fair enough. Let's turn to the body of</p> <p>2 your declaration. Let's start on page 2,</p> <p>3 paragraph 10. Let me know when you're there?</p> <p>4 A. I'm there.</p> <p>5 Q. Okay. You say here, "I have treated</p> <p>6 thousands of patients with pulmonary hypertension or</p> <p>7 PH, including PH associated with interstitial lung</p> <p>8 disease PHLD, and I have prescribed therapies</p> <p>9 including treprostinil to many of these patients. In</p> <p>10 particular I treat more than 100 patients with PHILD</p> <p>11 every year and I regularly prescribe the use of</p> <p>12 inhalers to my patients."</p> <p>13 Did I read that correctly?</p> <p>14 A. Yes.</p> <p>15 Q. Now, when you say, "in particular I treat</p> <p>16 more than 100 patients with PHILD every year", is</p> <p>17 that true this year?</p> <p>18 A. This year, 2024?</p> <p>19 Q. Correct.</p> <p>20 A. Well, we're only a few months into 2024.</p> <p>21 Q. Okay. In the last calendar -- strike that.</p> <p>22 In the last 12 months approximately how many patients</p> <p>23 with PHILD have you treated?</p> <p>24 A. Probably 100.</p> <p>25 Q. Okay. Are you familiar with a condition</p>	<p>24</p> <p>1 vessel becomes thickened and in some cases that can</p> <p>2 lead to pulmonary hypertension. So the very broad</p> <p>3 definition of PHILD is pulmonary hypertension that a</p> <p>4 clinician feels is due to the interstitial lung</p> <p>5 disease and not due to something else.</p> <p>6 Q. And what degree of lung disease do you need</p> <p>7 to see before you would characterize a patient as</p> <p>8 having PHILD as opposed to, for example, just PIH or</p> <p>9 Pulmonary Arterial Hypertension?</p> <p>10 MR. SUKDUANG: Objection. Vague.</p> <p>11 THE WITNESS: There is not a specific cut</p> <p>12 off in terms of the severity of interstitial lung</p> <p>13 disease that you need to cause pulmonary</p> <p>14 hypertension.</p> <p>15 Q. In your practice, what level of</p> <p>16 interstitial lung disease do you need to see before</p> <p>17 you'll categorize a patient as having PHILD?</p> <p>18 A. I don't have a specific cut off. It's more</p> <p>19 complex than that, unfortunately.</p> <p>20 Q. As part of your analysis in this case, what</p> <p>21 definition of PHILD did you apply?</p> <p>22 A. My clinical diagnoses of PHILD was the</p> <p>23 definition that the patient has interstitial lung</p> <p>24 disease that I feel is causing pulmonary</p> <p>25 hypertension. If I have a patient like that, based</p>

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<p style="text-align: right;">25</p> <p>1 on my 30 some years of experience, I make a 2 determination -- and I don't find another cause for 3 the pulmonary hypertension like illicit drug use or 4 left sided heart disease or blood clots in the lungs, 5 then I may make the diagnose of ILDPH. 6 Q. Let's go to paragraph 11, which is on the 7 next page of your declaration. You mention here that 8 you're the co-chair of the task force for the 7th 9 World Symposium on Pulmonary Hypertension charged 10 with advising the criteria for diagnosing PHILD. Do 11 you see that? 12 A. Yes. 13 Q. What is the World Symposium on Pulmonary 14 Hypertension? 15 A. The World Symposium is a regularly held 16 meeting typically every five years or so, where world 17 experts are invited to serve on various task forces 18 to come up with recommendations related to pretty 19 much all aspects of Pulmonary Hypertension. 20 Q. And clinically for doctors like yourself, 21 what is the significance of a recommendation that 22 would come out of the World Health Symposium on 23 Pulmonary Hypertension? 24 A. Well, for doctors like myself who are 25 experts in Pulmonary Hypertension, we're the ones</p>	<p style="text-align: right;">27</p> <p>1 the world's experts on Pulmonary Hypertension? 2 A. Like I said, it's invitation. People who 3 have a lot of expertise and experience. Sure. 4 Q. And you said that you are the co-chair of 5 the task force for PHILD at the 7th World Symposium; 6 is that correct? 7 A. Yes, that's the upcoming symposium, that's 8 June/July. 9 Q. Forgive me if you said this before, but how 10 often does the World Symposium meet? 11 A. It's about every five years. We delayed it 12 a year for this one, but in general that's about 13 right. 14 Q. Okay. When was the last symposium? The 15 6th World Symposium to your knowledge? 16 A. I believe it was in 2018. 17 Q. Okay. Let's go to paragraph 12 of your 18 declaration. You say, "since 1988, I have published 19 over 150 original articles in peer reviewed journals 20 including many on PH. Several of these articles 21 concern the treprostinil to treat PH including, for 22 example, on using inhaled treprostinil in group 3PH 23 patients." 24 Did I get that right? 25 A. Yes.</p>
<p style="text-align: right;">26</p> <p>1 developing the recommendations. The recommendations 2 are meant for people who aren't necessarily experts 3 in the field, and that's why this is sort of a 4 rather, you know, small group of world experts. We 5 come up with recommendations that we then publish and 6 people can read about. 7 Q. And these recommendations are meant for -- 8 strike that. Who are the recommendations from the 9 World Symposium meant for? 10 A. Well, they're -- as with any article, 11 they're meant for whoever reads them and wants to, 12 you know, look at them. I don't think I can be any 13 more specific than that. 14 Q. Sure. I'm just trying to get a sense of 15 how important these recommendations are to an 16 ordinary practicing pulmonologist? 17 A. That would be hard for me to answer the way 18 you asked it. It's very vague. How important? And 19 you're being so broad. Like, the whole document? I 20 mean, I think you would have to go through specific 21 comments or recommendations and I could certainly 22 address what I think about each of those, but I can't 23 give you a broad answer like that. 24 Q. Okay. But I think we can agree that the 25 World Symposium, as I think you said, is composed of</p>	<p style="text-align: right;">28</p> <p>1 Q. What are group 3PH patients? 2 A. That's again, Pulmonary Hypertension due to 3 lung or respiratory disease. That's the official 4 title of that group. 5 Q. Is PHILD a subset of group 3PH? 6 A. Yes. 7 Q. And you cite here -- you have a footnote 1 8 here. You cite to an article by Saggar et al, in 9 which you're the second author; is that correct? 10 A. Third author. 11 Q. Third author. Apologies. Aside from the 12 Saggar article that you've cited here, do you have 13 any other research articles regarding the use of 14 treprostinil in group 3 patients? 15 A. Not specifically, no. 16 Q. Okay. Is the Saggar 2021 article a peer 17 reviewed article? 18 A. Yes, it is. 19 Q. Dr. Channick, the court reporter's handed 20 you what's been marked Exhibit 2. 21 (Exhibit 2 marked for identification.) 22 Q. Do you recognize Exhibit 2? 23 A. Yes. 24 Q. What is it? 25 A. It's letters to the editor related to the</p>

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<p>29</p> <p>1 INCREASE study publication.</p> <p>2 Q. What's a letter to the editor?</p> <p>3 A. It's a letter to the editor.</p> <p>4 Q. Sure. For those of us who don't regularly</p> <p>5 practice and write to the New England Journal, what</p> <p>6 is the purpose of a letter to the editor?</p> <p>7 A. There is not one purpose for a letter to</p> <p>8 the editor. It's, in general, a letter that will</p> <p>9 discuss any number of things related to the article</p> <p>10 in question.</p> <p>11 Q. Okay.</p> <p>12 A. I can't be more specific than that.</p> <p>13 Q. Sure. Okay. And if you turn to the second</p> <p>14 page of Exhibit 2, in the second column do you see,</p> <p>15 "to the editor, Waxman and co-authors report</p> <p>16 favorable outcomes." Do you see that?</p> <p>17 A. Yes.</p> <p>18 Q. Okay. And then on the next column there</p> <p>19 are a list of authors?</p> <p>20 A. Yes.</p> <p>21 Q. And you are the third author?</p> <p>22 A. Yes.</p> <p>23 Q. Is this the publication, this letter to the</p> <p>24 editor that you're referring to in footnote 1 of your</p> <p>25 declaration?</p>	<p>31</p> <p>1 your CV, you have a section titled,</p> <p>2 "publications/bibliography". Do you see that?</p> <p>3 A. Yes.</p> <p>4 Q. And this is a list of your publications,</p> <p>5 editorials, book chapters, reviews, and what not?</p> <p>6 A. Yes.</p> <p>7 Q. The first section is, "research papers-peer</p> <p>8 reviewed"; is that correct?</p> <p>9 A. Yes.</p> <p>10 Q. And if you turn to page 28, there are</p> <p>11 approximately 169 articles listed in this section; is</p> <p>12 that correct?</p> <p>13 A. Yes.</p> <p>14 Q. Okay. And if we go to entry 143 on</p> <p>15 page 25, let me know when you're there.</p> <p>16 A. Yes.</p> <p>17 Q. Is this a reference to Exhibit 2, the New</p> <p>18 England Journal of Medicine letter to the editor that</p> <p>19 we just looked at?</p> <p>20 A. Yes.</p> <p>21 Q. Aside from entry 143, approximately how</p> <p>22 many publications in this section of your CV have to</p> <p>23 do with group 3PH?</p> <p>24 A. I'd have to go through and look. I think</p> <p>25 -- if you want me to, I'm happy to. Do you want me</p>
<p>30</p> <p>1 A. Yes.</p> <p>2 Q. Now, this letter to the editor, was this</p> <p>3 peer reviewed before it was published in the New</p> <p>4 England Journal?</p> <p>5 A. Yes. Letters to the editors are typically</p> <p>6 reviewed. It's not automatically published. Many</p> <p>7 letters are written that are not published. So</p> <p>8 they're certainly reviewed and chosen.</p> <p>9 Q. So when you say, "They're peer reviewed",</p> <p>10 they're selected -- are you getting proposed</p> <p>11 revisions from referees or reviewers of letters to</p> <p>12 the editor, or is it just a selection process?</p> <p>13 A. Different journals work differently. I</p> <p>14 can't recall in this particular case with the New</p> <p>15 England Journal whether we had any suggested changes</p> <p>16 made or corrections, or whether we were just chosen.</p> <p>17 I honestly don't remember.</p> <p>18 Q. Okay. And this letter to the editor</p> <p>19 concerns the INCREASE trial, and more specifically</p> <p>20 the publication regarding the INCREASE trial by</p> <p>21 Waxman et al; correct?</p> <p>22 A. Yes.</p> <p>23 Q. Okay. You can put that aside for now. I'd</p> <p>24 like to go back to Appendix B of your report, Dr.</p> <p>25 Channick, which is your CV. If you go to page 12 of</p>	<p>32</p> <p>1 to identify each one?</p> <p>2 Q. That would be quite helpful. Thank you.</p> <p>3 A. Number 11. I believe number 15.</p> <p>4 Q. Okay.</p> <p>5 A. Number 26. 39, possibly. Includes group</p> <p>6 3, possibly. 55. Probably 63 as well. 142.</p> <p>7 Q. Is that 142?</p> <p>8 A. 142, correct. You mentioned 143 already.</p> <p>9 Q. Yup.</p> <p>10 A. 169 would be as well.</p> <p>11 Q. Okay.</p> <p>12 A. That's it for the original.</p> <p>13 Q. Okay. So just so I understand, you</p> <p>14 identified 11, 15, 26, 39 as a maybe, 55, 63, 142,</p> <p>15 143, and 169; is that correct?</p> <p>16 A. Yes.</p> <p>17 Q. Okay. Next section, "book chapters".</p> <p>18 Approximately how many of the book chapters you've</p> <p>19 listed here, I believe there's 17 of them, deal with</p> <p>20 group 3PH?</p> <p>21 A. This is way back, but probably number 5 and</p> <p>22 probably number 7. Probably 8 and 9. These are all</p> <p>23 reviewed chapters on Pulmonary Hypertension, so they</p> <p>24 likely discuss group 3 within them.</p> <p>25 Q. Okay.</p>

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<p>33</p> <p>1 A. Everything in here that says pulmonary 2 hypertension that's a review article or chapter is 3 probably going to include a review of group 3 most 4 likely. 5 Q. Okay. Are any of these chapters that 6 you're reviewing specifically directed to group 3 or 7 PHILD? 8 A. No. 9 Q. Okay. The next section is "review 10 articles". Do you see you list 16 of those? 11 A. Yes. 12 Q. What's the difference between a review 13 article and an original research paper? 14 A. A review article reviews a topic. It 15 usually isn't a typical research study with 16 hypotheses, methods, results, conclusions. It 17 basically reviews a topic. It can be peer reviewed, 18 but not always. Sometimes it's an invited review. 19 That's probably the best way to put it. 20 Q. Sure. Of the 16 -- apologies. Strike 21 that. Of the 16 reviews you've listed in your CV, 22 approximately how many directly relate to group 3 or 23 PHILD? 24 A. It looks like number 3 is a review based on 25 the previous paper of pulmonary fibrosis. So</p>	<p>35</p> <p>1 Q. And what were the results of those trials, 2 to your knowledge? 3 A. I think there were mixed results. It was 4 an early trial that showed benefit, and then other 5 trials showed less benefit for different end points. 6 So I think there were mixed results. 7 Q. All right. Let's go back to the body of 8 your declaration, in particular paragraph 52. Are 9 you there? 10 A. Yes. 11 Q. I'd like to start with the third sentence. 12 You say, "I, for example, started prescribing Tyvaso 13 to PHILD patients almost immediately after it was 14 approved in 2009, and I did so according to the 15 dosing register men described in the Tyvaso label." 16 Did I read that correctly? 17 A. Yes. 18 Q. So between 2009 and -- strike that. 19 Between the approval of Tyvaso in 2009 up until 20 April 2020, approximately how many PHILD patients did 21 you treat with Tyvaso? 22 A. It's a very rough estimate. We're probably 23 talking 50 or more. 24 Q. And at that time, Tyvaso was not approved 25 for the treatment of PHILD; is that correct?</p>
<p>34</p> <p>1 probably number 3 would be the only one. 2 Q. I notice review article number 3 as well as 3 several of the original research articles you 4 referenced had to do with the use of inhaled nitric 5 oxide for treatment of pulmonary hypertension; is 6 that right? 7 A. Yes. 8 Q. Can you give a brief description of your 9 work in that space? 10 A. Yeah. So going way back to the early 90s 11 when we started studying the use of inhaled nitric 12 oxide, which is a pulmonary evasive dilator drug. We 13 studied it in patients with Pulmonary Hypertension 14 and published a very early work on using it as a 15 therapy for Pulmonary Hypertension, including 16 Pulmonary Hypertension due to interstitial lung 17 disease. 18 Q. And has the use of inhaled nitric oxide for 19 Pulmonary Hypertension ever been the subject of a 20 placebo controlled clinical trial? 21 A. Yes. 22 Q. What trials were those, to your knowledge? 23 A. I can't remember the name of the trial, but 24 there was certainly one trial, a couple trials done 25 with inhaled NO.</p>	<p>36</p> <p>1 A. Correct. 2 Q. So you would characterize this as off label 3 treatment? 4 A. Yeah, it's hard to -- I know you want to 5 sort of itemize it. But as we said, the PHILD 6 diagnosis, there's a lot of overlap with, what we 7 call, group 1 and group 3, and any expert will tell 8 you that. And so what constitutes off label use 9 versus, you know, more on label use can be a real 10 judgment call. I mean, that's the best way I can say 11 it. 12 If you're going to dichotomize it and 13 you're diagnosing someone as PHILD, you could call 14 that off label, but -- I apologize for giving a long 15 winded answer, but there are patients who have PHILD 16 but the PH is very severe and the ILD is less severe. 17 Those patients may be very similar to a patient that 18 we call group 1, in which case, although it's, quote, 19 off label, the patient is very similar to a group 1 20 patient. 21 So from a clinician's point of view, it's 22 more on label. I know it's a technicality, but -- 23 Q. Fair enough. So of the 50 plus patients 24 you mentioned, approximately how many of them were in 25 the category that you just mentioned that had a</p>

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<p>37</p> <p>1 predominantly group 1 phenotype but also had elements 2 of lung disease?</p> <p>3 A. I would say maybe 50/50. Again, it depends 4 how you define it. I'm sure we'll get into a lot 5 more detail on this, we're treating the Pulmonary 6 Hypertension, not the interstitial lung disease, with 7 Tyvaso. And so that's how we look at each patient 8 who has interstitial lung disease and Pulmonary 9 Hypertension. We ask ourselves, is this Pulmonary 10 Hypertension something we should be treating in this 11 patient?</p> <p>12 Is it causing their symptoms? Is it 13 contributing? These are obviously in detailed 14 evaluations we do.</p> <p>15 Q. But in your clinical judgment, you consider 16 all of those patients to be PHILD patients?</p> <p>17 A. Yes.</p> <p>18 Q. Dr. Channick, the court reporter's just 19 handed you what's been marked as Exhibit 3. I 20 realize the cover page says Exhibit 2. This is a 21 document bearing Bates numbers UTC_PH-ILD_010692 22 through 708. 23 (Exhibit 3 marked for identification.)</p> <p>24 Q. With the exception of the cover page, do 25 you recognize Exhibit 3?</p>	<p>39</p> <p>1 A. What the drug is approved for by the FDA. 2 Q. And as of 2009, what was Tyvaso approved 3 for? 4 A. The treatment of Pulmonary Arterial 5 Hypertension for group 1 in patients with near 6 (inaudible) Class 3 symptoms to increase walk 7 distance.</p> <p>8 Q. Does this 2009 label for Tyvaso mention 9 group 3 Pulmonary Hypertension or PHILD?</p> <p>10 A. Yes.</p> <p>11 Q. Where?</p> <p>12 A. It doesn't mention that specifically. Let 13 me make a small correction. It alludes to underlying 14 lung disease under warnings and precautions.</p> <p>15 Q. Are you referring to the bullet that reads, 16 and this is on Bates ending 693, "safety and efficacy 17 have not been established in patients with 18 significant underlying lung disease such as Asthma or 19 chronic obstructive Pulmonary Disease." Is 20 that what you were referring to?</p> <p>21 A. Yes.</p> <p>22 Q. And Chronic Obstructive Pulmonary Disease 23 is commonly referred to as COPD?</p> <p>24 A. Yes.</p> <p>25 Q. And a patient that has Pulmonary</p>
<p>38</p> <p>1 A. Yes.</p> <p>2 Q. What is Exhibit 3?</p> <p>3 A. It looks like the label for Tyvaso.</p> <p>4 Q. And in particular, which label for Tyvaso?</p> <p>5 A. What do you mean, "which label for Tyvaso"?</p> <p>6 Q. Strike that. What's the date on this 7 label?</p> <p>8 A. Well, it says, "revised July 2009". 9 There's 2002 under initial U.S. approval.</p> <p>10 Q. So this would have been the label or 11 prescribing information available for Tyvaso as of 12 July 2009; is that correct?</p> <p>13 A. Yes.</p> <p>14 Q. Generally, Dr. Channick, as a physician, 15 what's the purpose of the prescribing information or 16 what we've been calling the label for medication like 17 Tyvaso?</p> <p>18 A. It's to communicate the approved 19 indication, dosage, warnings, safety issues to help 20 guide clinicians.</p> <p>21 Q. You use the word "indication". What's an 22 indication in the context of a drug label?</p> <p>23 A. It relates to the -- at least in the U.S., 24 the FDA approved indication.</p> <p>25 Q. Okay.</p>	<p>40</p> <p>1 Hypertension and COPD would be a group 3 patient?</p> <p>2 A. If the clinician felt that Pulmonary 3 Hypertension was due to the COPD, yes. He would call 4 it group 3.</p> <p>5 Q. Okay. In other words, COPD is a form of 6 Interstitial Lung Disease or IOD; is that right?</p> <p>7 A. It's actually not. It's a lung disease, 8 but it's not an interstitial lung disease. It's a 9 disease of the air sacks like Emphysema, but it is a 10 lung disease. And so when you have Pulmonary 11 Hypertension due to that lung disease, including 12 COPD, it's called group 3.</p> <p>13 Q. Does this 2009 Tyvaso label state anywhere 14 that Tyvaso can be used to treat patients with PHILD?</p> <p>15 A. Can be used? I don't think the label gives 16 permission to use something in the way you're 17 referring to it. I guess I'm a little confused by 18 that question.</p> <p>19 Q. Does the label instruct doctors that Tyvaso 20 can or should be used for the treatment of group 3 21 Pulmonary Hypertension?</p> <p>22 A. Again, I'm going to be -- I don't 23 understand, instruct them that they can or should 24 use. It never says you should use a drug, a label. 25 It never says you can't use a drug for an indication</p>

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<p style="text-align: right;">41</p> <p>1 unless there's a contra indication, which I don't see</p> <p>2 here. So it doesn't say you can't use the drug.</p> <p>3 There's no contra indications, in fact. So I guess,</p> <p>4 again, it would say -- it doesn't instruct you not to</p> <p>5 use it for ILDPH.</p> <p>6 Q. But it does not affirmatively instruct the</p> <p>7 use of this drug for --</p> <p>8 A. I don't understand what you mean by,</p> <p>9 "affirmatively instruct".</p> <p>10 Q. Let me back up. That was a poor question</p> <p>11 and I apologize. The drug it says, is indicated for</p> <p>12 the treatment of PAH; right?</p> <p>13 A. Correct.</p> <p>14 Q. It does not state that the drug is FDA</p> <p>15 approved for the treatment of PHILD?</p> <p>16 A. Correct.</p> <p>17 Q. Okay. In this label, are there any safety</p> <p>18 or efficacy data discussing the use of Tyvaso in</p> <p>19 group 3 or PHILD patients?</p> <p>20 A. I'm sorry. You asked if there was any data</p> <p>21 specifically in that population.</p> <p>22 Q. Correct. Is there anything in this label</p> <p>23 that depicts the use of Tyvaso in a group 3 or a</p> <p>24 PHILD phenotype?</p> <p>25 A. Not other than the precaution about those</p>	<p style="text-align: right;">43</p> <p>1 Q. Generally, doctor, what was the subject of</p> <p>2 this article?</p> <p>3 A. This was basically a review of that topic,</p> <p>4 of Pulmonary Hypertension, non-PAH. So non-group 1.</p> <p>5 Q. Okay. And I see in the abstract there's a</p> <p>6 reference to the Fourth World Symposium on Pulmonary</p> <p>7 Hypertension. Why are you making a reference to the</p> <p>8 Fourth World Symposium here?</p> <p>9 A. Well, I certainly don't recall. I think it</p> <p>10 was highlighting that that -- just reading what it</p> <p>11 says here, that it was the first conference to focus</p> <p>12 on other causes of Pulmonary Hypertension besides</p> <p>13 PAH.</p> <p>14 Q. Now, does this article summarize the</p> <p>15 discussions of a working group from the Fourth World</p> <p>16 Symposium, or is it something different?</p> <p>17 A. This is basically the summary of the</p> <p>18 working group.</p> <p>19 Q. Okay. Of which you were a member?</p> <p>20 A. Yes.</p> <p>21 Q. I'd like you to turn to the page S87 at the</p> <p>22 top, please.</p> <p>23 A. Okay.</p> <p>24 Q. Do you see there's a heading on the bottom</p> <p>25 right that says, "treatment of PH with patients with</p>
<p style="text-align: right;">42</p> <p>1 particular patients.</p> <p>2 Q. Okay. We've been going for about an hour.</p> <p>3 Is now a good time for a break?</p> <p>4 A. Sure.</p> <p>5 VIDEOGRAPHER: We're going off the record.</p> <p>6 The time is 9:55 A.M.</p> <p>7 (Recess taken.)</p> <p>8 VIDEOGRAPHER: We're back on the record.</p> <p>9 The time is 10:08.</p> <p>10 Q. Okay. Welcome back, Dr. Channick. The</p> <p>11 court reporter's handed you what's been marked as</p> <p>12 Exhibit 4.</p> <p>13 (Exhibit 4 marked for identification.)</p> <p>14 Q. Do you recognize Exhibit 4?</p> <p>15 A. Yes.</p> <p>16 Q. What is Exhibit 4?</p> <p>17 A. This is an article that I'm one of the</p> <p>18 authors on titled, "diagnosis, assessment, and</p> <p>19 treatment of Non-Pulmonary Hypertension. Pulmonary</p> <p>20 Hypertension."</p> <p>21 Q. And what journal was this published in?</p> <p>22 A. Journal in the American College of</p> <p>23 Cardiology.</p> <p>24 Q. And the date is 2009; is that correct?</p> <p>25 A. Yes.</p>	<p style="text-align: right;">44</p> <p>1 chronic lung disease." Do you see that?</p> <p>2 A. Yes.</p> <p>3 Q. Would that include PHILD?</p> <p>4 A. Yes.</p> <p>5 Q. Do you see the third sentence of the first</p> <p>6 paragraph under that heading begins, so far?</p> <p>7 MR. SUKDUANG: I'm sorry. Say that one</p> <p>8 more time?</p> <p>9 Q. Sure. The paragraph under heading,</p> <p>10 treatment of PH in patients with chronic lung</p> <p>11 disease, the third sentence begins, so far. Do you</p> <p>12 see that?</p> <p>13 A. Yes.</p> <p>14 Q. Fourth sentence. Apologies. It reads, "so</p> <p>15 far, no large randomized control trials RCTs,</p> <p>16 addressing the long-term effects of drugs targeting</p> <p>17 PH have been formed in patients with chronic lung</p> <p>18 disease." Did I get that correctly?</p> <p>19 A. Yes.</p> <p>20 Q. And then going on to the last full sentence</p> <p>21 in the paragraph it says, "there is not sufficient</p> <p>22 evidence showing that drugs approved for the</p> <p>23 treatment of PAH, that is, endothelin receptor</p> <p>24 antagonists, ERAs, phosphodiesterase 5, or PBD 5</p> <p>25 inhibitors, and prostanoids are safe and effective in</p>

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<p style="text-align: right;">45</p> <p>1 patients with chronic lung disease associated PH." 2 Did I read that correctly? 3 A. Yes. 4 Q. And treprostinil is a prostanoid; is that 5 correct? 6 A. Yes. 7 Q. It goes on to the next page. It says, 8 "this is true for patients with advanced chronic lung 9 disease and mild PH as well as for patients with 10 severe PH in the setting of chronic lung disease, 11 independent of its severity." Did I get this 12 correct? 13 A. Yes. 14 Q. Next sentence reads, "any pulmonary 15 vasodilator that has the potential to worsen gas 16 exchange in patients with chronic lung disease and 17 the effects of these drugs may vary substantially 18 depending on whether the underlying disease has 19 obstructive or restrictive features." 20 Did I get that correct? 21 A. Yes. 22 Q. What is the difference between obstructive 23 or illusive lung disease? 24 A. Well, we kind of alluded to that before. 25 Obstructive would be like COPD, whether it's an</p>	<p style="text-align: right;">47</p> <p>1 associated with chronic lung disease." Did I get 2 that correct? 3 A. Yes. 4 Q. And the last bullet reads, "the use of 5 drugs currently approved for PAH in patients with 6 chronic lung disease is not recommended until further 7 data are available." Did I get that correct? 8 A. Yes. 9 Q. And those were the conclusions of the 10 Fourth World Symposium in 2009? 11 A. Yes, which was quite a while ago. 12 Q. So before the break and in your 13 declaration, you said that you prescribed Tyvaso 14 almost immediately after it was approved in 2009, 15 according to the label at that time; is that right? 16 A. Yes. 17 Q. And at that time in 2009, Tyvaso had only 18 been approved for the treatment of PAH; correct? 19 MR. SUKDUANG: Objection. Vague as to time 20 and the approval date of Tyvaso. 21 THE WITNESS: I would say that -- I don't 22 know the specific dates, and considering that when 23 this paper came out, when it would be written and 24 revised, I'm not sure, but I don't believe Tyvaso was 25 available at the time of this paper preparation but</p>
<p style="text-align: right;">46</p> <p>1 airway problem with airflow in the air sacs. 2 Restrictive is often interstitial lung disease. 3 Q. Okay. And the passage we just read, that 4 was the result -- strike that. That was the 5 conclusion of the working group of the Fourth World 6 Symposium on Pulmonary Hypertension; correct? As of 7 2009? 8 A. It was. I would want to say just to be 9 fair, that there was a sentence that you didn't read 10 after that that said, "short-term studies have been 11 performed in ILD patients with sildenafil, bosentan, 12 and inhaled iloprost, and these drugs had no adverse 13 effect on oxygenation." So we want to be balanced. 14 Q. Sure. Thank you. You see the next 15 sentence is entitled, "working group recommendations 16 for PH and chronic lung disease, COPD, ILD, and other 17 forms." Do you see that? 18 A. Yes. 19 Q. Okay. There's a section in the next column 20 that says, "treatment of PH in chronic lung disease." 21 Do you see that? 22 A. Yes. 23 Q. The second bullet reads, "there is no 24 sufficient evidence that the drugs currently used for 25 PAH are safe and effective in patients with PH</p>	<p style="text-align: right;">48</p> <p>1 we can certainly check on that. I don't believe that 2 to be the case. I think any recommendations you're 3 making did not take into account Tyvaso. 4 Q. Dr. Channick, the court reporter's handed 5 you what's been marked as Exhibit 5. 6 (Exhibit 5 marked for identification.) 7 Q. Do you recognize Exhibit 5? 8 A. Yes. 9 Q. What is Exhibit 5? 10 A. Exhibit 5 is an article entitled, "inhaled 11 treprostinil, a therapeutic review", of which I'm the 12 first author. 13 Q. In what journal was this review article 14 published in? 15 A. Drug Design Development and Therapy. 16 Q. This is a peer reviewed journal? 17 A. I'm not sure. Presumably. 18 Q. And your co-authors on this paper were 19 Robert Voswinkel and Lewis J. Rubin; is that correct? 20 A. Correct. 21 Q. Generally, what was the purpose of this 22 review article entitled, "inhaled treprostinil, a 23 therapeutic review"? 24 A. The purpose? I'm not sure -- 25 Q. Strike that. Why did you write this review</p>

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<p style="text-align: right;">49</p> <p>1 article?</p> <p>2 A. I don't recall. It could have been that I</p> <p>3 was asked to write it or invited to write it.</p> <p>4 Usually, as I mentioned earlier, with a review</p> <p>5 article it's often what we call an invited review.</p> <p>6 That the publisher asked you to write an article.</p> <p>7 But I certainly don't recall in this particular case.</p> <p>8 Q. In particular, this review article relates</p> <p>9 to the clinical use of inhaled treprostinil; is that</p> <p>10 correct?</p> <p>11 A. Correct.</p> <p>12 Q. And inhaled treprostinil, when was that</p> <p>13 first approved?</p> <p>14 A. 2009.</p> <p>15 Q. Okay. So is it fair to say that this is a</p> <p>16 review of the clinical use of treprostinil between</p> <p>17 the approval in 2009 and the date of this article,</p> <p>18 which would be 2012?</p> <p>19 A. Yeah. I'd have to go through and look at</p> <p>20 the specifics since it's been so long, but it looks</p> <p>21 like it's a therapeutic review. So review of the</p> <p>22 uses of inhaled treprostinil. Correct.</p> <p>23 Q. Doctor, you can feel free to take as much</p> <p>24 time as you want. At the time you wrote -- strike</p> <p>25 that. At the time you wrote this article, were you</p>	<p style="text-align: right;">51</p> <p>1 Q. Did you mention use of Tyvaso for PHILD by</p> <p>2 any other clinicians in this review article?</p> <p>3 A. Likely not, but I can look through it. It</p> <p>4 wouldn't be something I would do as well. When</p> <p>5 you're writing a review article such as this, you're</p> <p>6 reviewing published data. You're not giving your own</p> <p>7 personal approach as an expert in the field. There</p> <p>8 are other articles that one could do that if they</p> <p>9 wanted to, but I certainly wouldn't typically do this</p> <p>10 in a review article like this.</p> <p>11 Q. You mentioned that there are other forums</p> <p>12 by which this information could be divulged. Did you</p> <p>13 publish any articles about your use of Tyvaso in</p> <p>14 group 3 patients?</p> <p>15 A. No.</p> <p>16 Q. Can you turn to the page 25 of this</p> <p>17 article, Exhibit 5, please?</p> <p>18 A. Okay.</p> <p>19 Q. Do you see there's a heading that says,</p> <p>20 "warnings and precautions"?</p> <p>21 A. Yes.</p> <p>22 Q. It says, "safety and efficacy have not been</p> <p>23 established in patients with significant underlying</p> <p>24 Lung Disease such as Asthma or Chronic Obstructive</p> <p>25 Pulmonary Disease." Do you see that?</p>
<p style="text-align: right;">50</p> <p>1 prescribing Tyvaso to PHILD patients?</p> <p>2 A. Most likely, as I mentioned earlier.</p> <p>3 Q. In your therapeutic review of inhaled</p> <p>4 treprostinil in 2012, do you mention that use</p> <p>5 anywhere in this review?</p> <p>6 A. Mention my personal use in our patient</p> <p>7 population? Is that what you're asking?</p> <p>8 Q. Correct.</p> <p>9 A. I think it would -- I could look through</p> <p>10 it, but it certainly wouldn't be my custom and</p> <p>11 practice to give personal anecdotes about my use as</p> <p>12 an expert in PH when I'm writing a review article</p> <p>13 that's meant for a large readership that may be</p> <p>14 not -- PH center.</p> <p>15 So I think you have to make a big</p> <p>16 distinction between expert who sees patients all the</p> <p>17 time and does nothing but this and a use of a drug,</p> <p>18 and what you put into a review that will go far and</p> <p>19 wide to general practitioners, general internists,</p> <p>20 general practitioners, general internists, general</p> <p>21 pulmonologists. It's a big difference. I think it</p> <p>22 would be unlikely, and I'll look through and confirm</p> <p>23 that, that i would say, oh, I'm using this in</p> <p>24 selected patients with PHILD. That would not be what</p> <p>25 I would typically do in a review article.</p>	<p style="text-align: right;">52</p> <p>1 A. Yes.</p> <p>2 Q. And that was correct when you wrote it in</p> <p>3 2012?</p> <p>4 A. Yes, this looks like it comes right out of</p> <p>5 the label word for word, that we talked about</p> <p>6 already.</p> <p>7 Q. Doctor, in 2012 when you prescribed Tyvaso</p> <p>8 to a PHILD patient, did you inform them that the</p> <p>9 safety and efficacy of that medication had not been</p> <p>10 established in patients with significant underlying</p> <p>11 Lung Disease?</p> <p>12 A. I discuss risks and benefits of every drug</p> <p>13 with every patient. So no doubt I would discuss</p> <p>14 what's known, what's not known, risks and benefits.</p> <p>15 That's what I've done my entire practice.</p> <p>16 Q. You can put that aside. Dr. Channick, the</p> <p>17 court reporter's handed you what's been marked as</p> <p>18 Exhibit 6.</p> <p>19 (Exhibit 6 marked for identification.)</p> <p>20 Q. The first page is a screenshot from YouTube</p> <p>21 of a video --</p> <p>22 A. Not my best picture.</p> <p>23 Q. It's from the, "I'm aware that I'm rare,</p> <p>24 the PH aware podcast, episode 71, Richard N Channick</p> <p>25 MD, uploaded to YouTube June 26th of 2017." And then</p>

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<p>53</p> <p>1 after that, you can see that there's a transcript of 2 that video. Dr. Channick can you -- 3 MR. SUKDUANG: Hold on counsel. I'll just 4 note for the record, there's nothing on the document, 5 the exhibit, verifying your statements as to what 6 this is and where it is. Go ahead. 7 MR. ROMEO: Okay. I think there's a URL on 8 the first page, but -- 9 MR. SUKDUANG: But it doesn't have the 10 date. It doesn't have where it is. It just hands 11 random cues and whatever. But you can go ahead. 12 Just putting for the record. 13 Q. Dr. Channick, do you recall participating 14 in the PH aware podcast in 2017? 15 A. I'm aware of the PH aware platform and have 16 definitely contributed to that platform. 17 Q. What is the PH aware platform? 18 A. It's a platform that is geared, I think, 19 mainly towards patients where experts are interviewed 20 about various aspects of Pulmonary Hypertension. I 21 think the target is mainly patients with Pulmonary 22 Hypertension. 23 Q. And do you recall recording this podcast 24 episode in 2017? 25 A. Not specifically, no. Like I said, I've</p>	<p>55</p> <p>1 treatment, get it approved and get it to patients, is 2 by doing properly conducted clinical trials." Did I 3 read that correctly? 4 A. Yes. 5 Q. What's a properly conducted clinical trial? 6 A. Well, it's a study where there's proper 7 conduct, that you have a design, you have appropriate 8 informed consent, you have methodology that's 9 accepted. It's meant as sort of a general term as 10 opposed to improperly conducted clinical trial. I 11 wouldn't read more into it than that. 12 Q. Okay. In that methodology you mentioned, 13 would that include placebo control? 14 A. Well, it depends on where in the clinical 15 trial development, and we can get into drug 16 development if you like, but you often have a phase 2 17 clinical trial that may or may not have a placebo. 18 Typically for FDA approval specifically, with rare 19 exception, a placebo controlled trial is required. 20 Q. If you could turn to the next page of the 21 transcript, page 2. I'd like to go to the sentence 22 beginning on line 17? 23 MR. SUKDUANG: Just for the record, it's 24 page 3. 25 MR. ROMEO: Page 3. Sorry, my fault. I</p>
<p>54</p> <p>1 done I think several of them. I don't remember this 2 one in particular. 3 Q. So if you just go to the first page of the 4 transcript it says -- let me know when you're there. 5 "I'm Richard Channick. I'm a pulmonary critical care 6 specialist and director of the Pulmonary Hypertension 7 program at the Massachusetts General Hospital in 8 Boston. Today, I'd like to talk a little bit about 9 clinical trials." Do you see that? 10 A. Yes. 11 Q. Were you employed at MGH in 2017? 12 A. Yes. 13 Q. Okay. Does this refresh your recollection 14 as to the subject of this podcast? 15 A. Not specifically, but like I said, I've 16 given several podcasts. I just don't remember this 17 specifically. 18 Q. Okay. Line 7 on page 1 says, "the only way 19 one can get a new treatment, get it approved, and get 20 it to patients is by doing a properly conducted" -- 21 strike that. "By doing properly conducted clinical 22 trials." Do you see that? 23 A. Yes. 24 Q. I'll read it again. Let me start over. 25 Line 7, it begins, "the only way one can get a new</p>	<p>56</p> <p>1 think I'm looking at a different version than you, 2 but I apologize. So page -- 3 MR. SUKDUANG: I just want to make sure 4 mine is -- 5 MR. ROMEO: Yes, correct. My apologies, 6 counsel. The version that I have highlighted is not 7 the version with the time stamps, which is the one 8 you have. 9 Q. Okay. Let's go to page 3 of the 10 transcript, line 17. You say here, "so patients need 11 to understand that usually by the point that a drug 12 gets to a certain phase in the clinical trial 13 development, we call it phase 3. There's some pretty 14 good evidence that the drug has benefit but we need 15 to do these bigger trials, phase 3 trials to really 16 prove that." Do you see that? 17 A. Yes. 18 Q. So why is it important to perform a phase 3 19 trial to really prove that a drug works? 20 MR. SUKDUANG: Objection. Vague. 21 THE WITNESS: As I said, the purpose of the 22 phase 3 trial is to get the drug approved. The FDA 23 typically requires a phase 3 trial to approve a drug. 24 So that's why the drug development phase, and we're 25 talking about experimental drugs, so never been</p>

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<p style="text-align: right;">57</p> <p>1 approved. It's like a molecule. You need to -- the</p> <p>2 FDA standards have a randomized control trial to get</p> <p>3 the drug approved. That's called phase 3.</p> <p>4 Q. When you say, "a randomized control trial",</p> <p>5 what do you mean?</p> <p>6 A. It means that patients are assigned to</p> <p>7 either get the active drug, experimental drug, let's</p> <p>8 say, that you are studying, or not. Oftentimes that</p> <p>9 would not include a placebo so that the patient and</p> <p>10 the investigator might not know what they are on</p> <p>11 whether it's the drug or the placebo. There are</p> <p>12 control trials where you don't give a placebo and</p> <p>13 they're still called randomized control trials, which</p> <p>14 is a control group.</p> <p>15 Q. Doctor, in your experience, have you</p> <p>16 encountered a situation where a drug showed promise</p> <p>17 in the phase 2 trial and it did not succeed at phase</p> <p>18 3?</p> <p>19 A. Yes.</p> <p>20 Q. Approximately how many times have you</p> <p>21 encountered that in your career?</p> <p>22 A. I mean, I've been very focused on Pulmonary</p> <p>23 Hypertension. I'm sure there's numerous examples in</p> <p>24 other disease states. Probably a couple. I'd say</p> <p>25 two or three, maybe. Again, we're talking about</p>	<p style="text-align: right;">59</p> <p>1 Q. And why is it important to have appropriate</p> <p>2 inclusion and exclusion criteria when designing a</p> <p>3 clinical trial?</p> <p>4 A. In general, and I don't want to get too</p> <p>5 into the weeds here with clinical trial development,</p> <p>6 but in general when we're designing a study, we want</p> <p>7 to give it the maximum likelihood of success. And</p> <p>8 often, for instance, you want a relatively homogenous</p> <p>9 group that shares features rather than risk having a</p> <p>10 very heterogeneous group that might not share a lot</p> <p>11 of features, in which case it may lower the</p> <p>12 likelihood of success for the trial.</p> <p>13 Q. So fair to say that the inclusion and</p> <p>14 exclusion criteria of a particular trial could impact</p> <p>15 the ultimate result?</p> <p>16 A. Yes.</p> <p>17 Q. Next you say, "we can't, for instance, take</p> <p>18 a treatment and apply it to every patient with</p> <p>19 Pulmonary Hypertension. We know very clearly and</p> <p>20 have clear experience that drugs that work for some</p> <p>21 forms of Pulmonary Arterial Hypertension won't work</p> <p>22 and in fact can make things worse." Did I get that</p> <p>23 right?</p> <p>24 A. Yes.</p> <p>25 Q. What drugs in particular are you referring</p>
<p style="text-align: right;">58</p> <p>1 experimental therapies that are not approved.</p> <p>2 Q. If you could go to page 4 of the</p> <p>3 transcript, please.</p> <p>4 A. Okay.</p> <p>5 Q. Line 7 you say, "and with Pulmonary</p> <p>6 Hypertension, it's complex because Pulmonary</p> <p>7 Hypertension is not one disease. It's many</p> <p>8 diseases." Do you see that?</p> <p>9 A. Yes.</p> <p>10 Q. What do you mean that "Pulmonary</p> <p>11 Hypertension is many diseases"?</p> <p>12 A. Pulmonary Hypertension is not a disease,</p> <p>13 it's a number. It means that the pressure is above a</p> <p>14 certain level. It doesn't tell you what's causing</p> <p>15 that high pressure. Many different diseases can</p> <p>16 cause that high pressure.</p> <p>17 Q. Okay. And then you go on to say, "when</p> <p>18 we're trying to design inclusion and exclusion</p> <p>19 criteria, we have to take that into account." Did I</p> <p>20 get that right?</p> <p>21 A. Yes.</p> <p>22 Q. What are inclusion and exclusion criteria?</p> <p>23 A. They're a list of criteria that are either</p> <p>24 required for a patient to be eligible for the study,</p> <p>25 or exclude them from being part of the study.</p>	<p style="text-align: right;">60</p> <p>1 to there?</p> <p>2 A. I don't recall what I was referring to</p> <p>3 there. In this particular podcast -- again, this is</p> <p>4 a podcast for patients, and we're making obviously</p> <p>5 very broad points and cautioning patients about, and</p> <p>6 explaining the whole drug development process and how</p> <p>7 drugs get approved by the FDA for instance. So I</p> <p>8 certainly can't sit here today and say what specific</p> <p>9 drugs I was talking about in this podcast.</p> <p>10 Q. That statement was true when you made it in</p> <p>11 2017; correct?</p> <p>12 A. Yes. That general statement. We know that</p> <p>13 some drugs that work for some forms of PH don't work</p> <p>14 for others and can make things worse. That's</p> <p>15 absolutely true.</p> <p>16 Q. All right. If you could go to page 16 of</p> <p>17 the transcript. This is just for my own curiosity,</p> <p>18 Doctor.</p> <p>19 MR. SUKDUANG: There's no page 16.</p> <p>20 MR. ROMEO: It's page -- sorry. I</p> <p>21 apologize. Page 7. Page 7 and 8. I apologize. I</p> <p>22 was looking at my version.</p> <p>23 Q. On line 22, page 7 into page 8, you</p> <p>24 conclude the webinar by saying, "my name is Rich</p> <p>25 Channick and I'm aware that I'm rare." What is that</p>

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<p>61</p> <p>1 a reference to?</p> <p>2 A. That's their motto for the PH aware. I do</p> <p>3 remember that. They always make you end it with that</p> <p>4 kind of goofy statement.</p> <p>5 Q. So what does that refer to? Is that to the</p> <p>6 patients or to you?</p> <p>7 MR. SUKDUANG: Asked and answered.</p> <p>8 THE WITNESS: I believe it refers to the</p> <p>9 patients are rare. A rare condition.</p> <p>10 Q. Okay.</p> <p>11 A. Not me specifically.</p> <p>12 Q. That was my assumption, but I just wanted</p> <p>13 to ask. Okay. Let's go to Tab 170, please. Dr.</p> <p>14 Channick, the court reporter's handed you what's been</p> <p>15 marked as Exhibit 7.</p> <p>16 (Exhibit 7 marked for identification.)</p> <p>17 Q. This is an article published in the -- I</p> <p>18 believe the European Respiratory Journal in 2019</p> <p>19 entitled, "Pulmonary Hypertension and chronic lung</p> <p>20 disease and Hypoxia". Do you recognize Exhibit 7?</p> <p>21 A. Yes.</p> <p>22 Q. When was the first time you saw Exhibit 7?</p> <p>23 A. Likely as soon as it was published.</p> <p>24 Q. Why is that?</p> <p>25 A. Excuse me?</p>	<p>63</p> <p>1 Q. Is the first named author on this paper</p> <p>2 Steven D Nathan?</p> <p>3 A. Yes.</p> <p>4 Q. You know Dr. Nathan?</p> <p>5 A. Yes.</p> <p>6 Q. How long have you known Dr. Nathan?</p> <p>7 A. At least a few decades.</p> <p>8 Two-and-a-half-decades. I don't know. A long time.</p> <p>9 Q. And have you interacted with Dr. Nathan in</p> <p>10 connection with the World Symposium on Pulmonary</p> <p>11 Hypertension?</p> <p>12 MR. SUKDUANG: Objection. Vague.</p> <p>13 THE WITNESS: I saw him at the meeting, at</p> <p>14 this meeting, I'm sure. We weren't on the same</p> <p>15 committee.</p> <p>16 Q. Okay. And in what context have you</p> <p>17 interacted with Dr. Nathan over the course of your</p> <p>18 career?</p> <p>19 A. Any number of contacts. I mean, we're in a</p> <p>20 relatively small group. So many meetings and</p> <p>21 symposia. You name it.</p> <p>22 Q. Do you consider Dr. Nathan to be a good</p> <p>23 doctor?</p> <p>24 MR. SUKDUANG: Objection. Vague.</p> <p>25 THE WITNESS: I'm not going to sit here and</p>
<p>62</p> <p>1 Q. I said, why is that?</p> <p>2 A. Why is what?</p> <p>3 Q. Why were you aware of it as soon as it was</p> <p>4 published?</p> <p>5 A. Because I read it.</p> <p>6 Q. Okay.</p> <p>7 A. This is the proceedings of the Sixth World</p> <p>8 Symposium to the last one before the one that we're</p> <p>9 working on now and I was part of the Sixth World</p> <p>10 Symposium. So I obviously was aware of this</p> <p>11 particular paper.</p> <p>12 Q. Okay. And when you say the proceedings of</p> <p>13 the Sixth World Symposium on Pulmonary Hypertension,</p> <p>14 what are you referring to?</p> <p>15 A. The meeting we talked about earlier. It's</p> <p>16 every five years. So meetings of experts in the</p> <p>17 field to develop recommendations in various areas.</p> <p>18 Q. Okay. Now, you're not an author on this</p> <p>19 paper; correct?</p> <p>20 A. Correct.</p> <p>21 Q. Are you familiar with any of the authors of</p> <p>22 this paper?</p> <p>23 A. Yes.</p> <p>24 Q. All of them?</p> <p>25 A. Yes.</p>	<p>64</p> <p>1 judge his clinical skills.</p> <p>2 Q. Do you have any concerns about his clinical</p> <p>3 skills?</p> <p>4 A. No.</p> <p>5 Q. Would you consider Dr. Nathan to be an</p> <p>6 expert in PHILD?</p> <p>7 A. He's certainly published a lot in the</p> <p>8 field, absolutely.</p> <p>9 Q. Does that make him an expert in PHILD?</p> <p>10 A. Yeah.</p> <p>11 Q. When Dr. Nathan publishes about PHILD, do</p> <p>12 you find him to be a credible voice in the field?</p> <p>13 A. Again, it's one of those vague questions.</p> <p>14 You have to give me specific comments. I'm not going</p> <p>15 to make a generic statement like that. Show me</p> <p>16 something he's wrote and I can tell you if I agree</p> <p>17 with it or not.</p> <p>18 Q. Doctor, if you could turn to page 8 of this</p> <p>19 article, Exhibit 7.</p> <p>20 A. Okay.</p> <p>21 Q. Do you see that there is a section on</p> <p>22 Idiopathic Interstitial Pneumonias?</p> <p>23 A. Yes.</p> <p>24 Q. Are Idiopathic Interstitial Pneumonias a</p> <p>25 form of ILD?</p>

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<p>65</p> <p>1 A. Yes.</p> <p>2 Q. Do you see here that there is a</p> <p>3 subparagraph entitled, "effect on pulmonary</p> <p>4 hemodynamics?</p> <p>5 A. Yes.</p> <p>6 Q. It says here, "uncontrolled studies have</p> <p>7 shown improvement in pulmonary hemodynamics in</p> <p>8 patients with IIPPH using Riociguat and treprostinil.</p> <p>9 However, RCTs have failed to substantiate such an</p> <p>10 improvement in this population." Did I get that</p> <p>11 correct?</p> <p>12 A. Yes.</p> <p>13 Q. Do you agree with that statement?</p> <p>14 A. No.</p> <p>15 Q. Why not?</p> <p>16 A. Because RCTs have shown improvement in this</p> <p>17 population.</p> <p>18 Q. Which RCTs in particular?</p> <p>19 A. INCREASE.</p> <p>20 Q. Okay. Was INCREASE complete as of 2019?</p> <p>21 A. No.</p> <p>22 Q. Okay. Let me re-ask the question. Would</p> <p>23 you have agreed -- strike that. Was this statement</p> <p>24 correct in 2019?</p> <p>25 A. Yes.</p>	<p>67</p> <p>1 encouraged." Did I get that right?</p> <p>2 A. Yes.</p> <p>3 Q. And treprostinil is a prostanoid therapy;</p> <p>4 correct?</p> <p>5 A. Yes.</p> <p>6 Q. And at the time this was written in 2017,</p> <p>7 treprostinil was only -- inhaled treprostinil was</p> <p>8 only approved for the treatment of PAH; is that</p> <p>9 correct?</p> <p>10 MR. SUKDUANG: Mischaracterizes. You said</p> <p>11 2017.</p> <p>12 MR. ROMEO: Strike that. Thank you,</p> <p>13 counsel.</p> <p>14 Q. When this was published in 2017 --</p> <p>15 MR. SUKDUANG: I'm sorry. I think you're</p> <p>16 still getting that wrong.</p> <p>17 MR. ROMEO: I apologize. Let me start</p> <p>18 again.</p> <p>19 Q. When this reference was published in 2019,</p> <p>20 inhaled treprostinil was only approved for the</p> <p>21 treatment of PAH; correct?</p> <p>22 A. Yes.</p> <p>23 Q. Okay. Was this conclusion correct when it</p> <p>24 was written in 2017? 2019. Apologies?</p> <p>25 MR. SUKDUANG: Objection. Vague.</p>
<p>66</p> <p>1 Q. Okay. And do you see here in talking about</p> <p>2 effect on pulmonary hemodynamics, there's references</p> <p>3 58 and 59?</p> <p>4 A. Yes.</p> <p>5 Q. If you could turn to page 14, please.</p> <p>6 A. Okay.</p> <p>7 Q. Do you recognize reference 59?</p> <p>8 A. Yes.</p> <p>9 Q. And that's an article by Saggar et al in</p> <p>10 thorax from 2014?</p> <p>11 A. Yes.</p> <p>12 Q. And that's an article you've cited in your</p> <p>13 declaration in this case?</p> <p>14 A. Yes.</p> <p>15 Q. Okay. Let's go back to page -- let's go to</p> <p>16 page 9, please. Do you see where there's a</p> <p>17 conclusion?</p> <p>18 A. Yes.</p> <p>19 Q. It says, "Riociguat and significant /KWRAT</p> <p>20 and Amber citizen tin are both contraindicated in</p> <p>21 IIPPH. There is no evidence of benefit for other</p> <p>22 endothelin receptor agonists in IIPPH. Data on the</p> <p>23 use of Sildenafil in IIPPH is conflicting, while</p> <p>24 evidence for prostanoid therapy is too limited for</p> <p>25 any other recommendations. Further RCTs are</p>	<p>68</p> <p>1 THE WITNESS: Which conclusion? You read</p> <p>2 several sentences.</p> <p>3 Q. Okay. The conclusion -- okay. Do you see</p> <p>4 that there is a conclusion listed on page 9 that</p> <p>5 consists of four sentences?</p> <p>6 A. Three sentences, maybe four.</p> <p>7 Q. Regardless of how many sentences there are,</p> <p>8 were these conclusions correct in 2017 --</p> <p>9 MR. SUKDUANG: Objection. --</p> <p>10 MR. ROMEO: 2019. Yes, I'll start again.</p> <p>11 Q. Were these conclusions correct in 2019?</p> <p>12 MR. SUKDUANG: Objection. Vague.</p> <p>13 THE WITNESS: I'm happy rather than going</p> <p>14 back and forth to just go through each one. The</p> <p>15 conclusion that Riociguat and ambrisentan are both</p> <p>16 contraindicated in IIPPH was correct and is correct.</p> <p>17 No benefit for endothelin receptor antagonists and</p> <p>18 IIPPH is correct. Data on the use of Sildenafil is</p> <p>19 conflicting, while evidence for prostanoid therapy is</p> <p>20 too limited for any current recommendations. I would</p> <p>21 say that's not correct at this point.</p> <p>22 And further RCPs are encouraged, certainly</p> <p>23 was correct back in 2019. Again, we're talking about</p> <p>24 a working group that's giving widespread</p> <p>25 recommendations for every physician who reads this.</p>

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<p>69</p> <p>1 This is, you know -- and so certainly those kinds of</p> <p>2 cautions and encouraging RCTs is part and parcel of</p> <p>3 these working groups and the kind of recommendations</p> <p>4 you give. So I would say in general those are</p> <p>5 correct statements at the time.</p> <p>6 Q. And as of 2019, the Sixth World Symposium</p> <p>7 working group recommended to physicians that evidence</p> <p>8 for prostanoid therapy is too limited for any current</p> <p>9 recommendations; is that correct?</p> <p>10 A. Yes. I mean, they weren't saying don't use</p> <p>11 it, never use it. They were just saying they</p> <p>12 couldn't give a recommendation to use it. Those are</p> <p>13 two very different things.</p> <p>14 The only thing they said don't use was</p> <p>15 Riociguat and ambrisentan.</p> <p>16 Q. You can put that aside. Dr. Channick, the</p> <p>17 court reporter's handed you what's been marked as</p> <p>18 Exhibit 8. This is the 2022 ESCERS guidelines for</p> <p>19 the diagnosis and treatment of Pulmonary Hypertension</p> <p>20 published in the European Heart Journal in 2022. Dr.</p> <p>21 Channick, have you seen Exhibit 8 before?</p> <p>22 A. Yes.</p> <p>23 Q. What is it?</p> <p>24 A. These are guidelines from the European</p> <p>25 Society of Cardiology and European Respiratory</p>	<p>71</p> <p>1 A. Yes.</p> <p>2 Q. Are you familiar with the ESCERS classes of</p> <p>3 recommendations?</p> <p>4 A. Yes.</p> <p>5 Q. And generally what's the purpose of</p> <p>6 classifying a recommendation with respect to the</p> <p>7 treatment of Pulmonary Hypertension?</p> <p>8 A. It's generally to provide guidance to</p> <p>9 clinicians who may not necessarily be experienced but</p> <p>10 who may have patients that they want to know about</p> <p>11 their disease and what to do with it, and it's an</p> <p>12 exercise by which one can rate, as I said, levels of</p> <p>13 evidence and provide recommendations that range from</p> <p>14 highly recommend, to definitely don't do it, kind of</p> <p>15 thing.</p> <p>16 Q. Sure. And so for example, class 1, the</p> <p>17 definition is, "evidence and/or general agreement</p> <p>18 that a given treatment or procedure is beneficial,</p> <p>19 useful, effective." Did I get that right?</p> <p>20 A. Yes.</p> <p>21 Q. And then the recommended wording for</p> <p>22 Class 1 is, "is recommended or is indicated"; is that</p> <p>23 right?</p> <p>24 A. Yes, which means that you should do it.</p> <p>25 Q. Yes. And that's why it's in green; right?</p>
<p>70</p> <p>1 Society in 2022.</p> <p>2 (Exhibit 8 marked for identification.)</p> <p>3 Q. And to your knowledge, what are the</p> <p>4 purposes of the ESCERS guidelines for the diagnosis</p> <p>5 and treatment of Pulmonary Hypertension?</p> <p>6 A. In general, guidelines such as this are</p> <p>7 supposed to be a sort of exhaustive review of</p> <p>8 available literature and data, and the very</p> <p>9 structured process for making recommendations that</p> <p>10 are evidence based related to pretty much every</p> <p>11 aspect of Pulmonary Hypertension.</p> <p>12 Q. When you say "evidence based", what do you</p> <p>13 mean?</p> <p>14 A. It means that there's evidence. I'm not</p> <p>15 sure what more I can say. You're evaluating</p> <p>16 evidence, judging the evidence, rating the evidence,</p> <p>17 and then giving recommendations based on it.</p> <p>18 Q. Okay. Could you turn to page 19 of</p> <p>19 Exhibit 8, please?</p> <p>20 A. Okay.</p> <p>21 Q. Do you see Table 3 says, "classes of</p> <p>22 recommendations"?</p> <p>23 A. Yes.</p> <p>24 Q. And there are five classes. 1, 2, 2A, 2B,</p> <p>25 and 3?</p>	<p>72</p> <p>1 A. Correct.</p> <p>2 Q. And Class 2. Class 2 says, "conflicting</p> <p>3 evidence and/or a divergence of opinion about the</p> <p>4 usefulness/efficacy of the given treatment or</p> <p>5 procedure." Did I get that right?</p> <p>6 A. Yes.</p> <p>7 Q. And then there are two sub classes here:</p> <p>8 Class 2A says, "weight of evidence/opinion is in</p> <p>9 favor of usefulness/efficacy", and then there's a</p> <p>10 light origin box that says, "should be considered";</p> <p>11 is that right?</p> <p>12 A. Yes.</p> <p>13 Q. And then Class B says, "usefulness/efficacy</p> <p>14 is less well established by evidence/opinion", and</p> <p>15 then there's a darker origin box that says, "may be</p> <p>16 considered"; is that right?</p> <p>17 A. Yes.</p> <p>18 Q. So as a -- strike that. You characterize</p> <p>19 Class 1 as something that I -- I don't have the real</p> <p>20 time, so I apologize if I got that wrong, but</p> <p>21 something that a pulmonologist should do, how would</p> <p>22 you characterize a Class 2A or Class 2B</p> <p>23 recommendation?</p> <p>24 A. Individual decisions that one should</p> <p>25 consider doing it. It's always tough in the middle.</p>

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<p style="text-align: right;">73</p> <p>1 I mean, the green says you really should do it and 2 then the red says you really shouldn't do it. And 3 there's everything else in between and that's where 4 judgment comes in, and some patients might benefit. 5 Some patients might not. 6 So you either should consider it -- 7 admittedly the difference between should and may is, 8 you know, I have the same confusion as you do. It's 9 just the matter of a gradient. Really, you should 10 consider it in these patients, and the orange is, you 11 could consider it in these patients. It's not 12 contraindicated. So the middle ones you would 13 consider on a case by case database, is how I would 14 interpret it. 15 Q. The final class, Class 3 says, "evidence or 16 general agreement that the given treatment or 17 procedure is not useful/effective and in some cases 18 may be harmful." Then there's a red box that says, 19 "is not recommended"; is that right? 20 A. Yes. 21 Q. And then underneath Table 3, do you see 22 Table 4 entitled, levels of evidence? 23 A. Yes. 24 Q. And these refer to levels of scientific 25 evidence; is that right?</p>	<p style="text-align: right;">75</p> <p>1 Q. And after treprostinil was -- inhaled 2 treprostinil was FDA approved for the treatment of 3 PHILD; correct? 4 MR. SUKDUANG: Objection. Vague. 5 THE WITNESS: When this article was 6 published, don't forget there's a lot that goes on 7 before it gets published, and the meeting might have 8 occurred before. I'd have to look at the dates. 9 Q. Okay. If you could turn to page 76, 10 please. Actually before we get there, let's go to 11 page 73. I apologize. Okay. Page 73, there's a 12 Section 9. It says, "Pulmonary Hypertension 13 associated with Lung Disease and/or Hypoxia (group 14 3)." Do you see that? 15 A. Yeah. Got it. 16 Q. And so this would include PHILD; correct? 17 A. Yes. 18 Q. And if you flip through the preceding 19 pages, there's an overview, sections on diagnosis, 20 therapy, et cetera; right? 21 A. Yes. 22 Q. Okay. And if we go to table -- page 76, I 23 apologize. There's recommendation Table 23. Do you 24 see that? 25 A. Yes.</p>
<p style="text-align: right;">74</p> <p>1 A. Correct. 2 Q. Okay. And there are three levels: A, B, 3 and C? 4 A. Yes. 5 Q. And A being the most evidence and C being 6 the least evidence; correct? 7 A. It's the quality of the evidence, not the 8 amount of the evidence. 9 Q. Can you explain? 10 A. So traditionally we talk about randomized 11 control trials that we talked about earlier, and 12 ideally multiple control trials are level A. Level B 13 is maybe one randomized control trial or 14 non-randomized trials if they are felt to be big 15 enough. Level C is the expert consensus, or maybe 16 small studies or retrospective studies. They're all 17 levels of evidence, meaning there is evidence, but 18 they sort of rate them. 19 Q. And these guidelines that we're looking at 20 in Exhibit 8, these were published in 2022; is that 21 correct? 22 A. Yes. 23 Q. So this would have been after the Increase 24 trial was published; right? 25 A. Yes.</p>	<p style="text-align: right;">76</p> <p>1 Q. And it says, "recommendations for Pulmonary 2 Hypertension associated with Lung Disease and/or 3 Hypoxia." Do you see there's a recommendation 4 Table 23A? 5 A. Yes. 6 Q. Okay. Do you see in the seventh row 7 there's a reference to inhaled treprostinil? 8 A. Yes. 9 Q. And that says, "inhaled treprostinil may be 10 considered in patients with PH associated with ILD." 11 Did I get that right? 12 A. Yes. 13 Q. And there's a reference there to reference 14 734; correct? 15 A. Yes. 16 Q. And if you turn to the back, I'll tell you 17 what page. To page 111. 18 A. Okay. 19 Q. What is reference 734? 20 A. That's the New England Journal publication 21 related to the Increase trial. 22 Q. And in particular that's a 2021 publication 23 by Waxman et al; correct? 24 A. Correct. 25 Q. And so with the INCREASE results in hand,</p>

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<p style="text-align: right;">77</p> <p>1 the ESCERS gave inhaled treprostinil in patients with 2 PH associated with ILD a Class 2B recommendation; is 3 that correct? 4 A. Yes. 5 Q. And a level B categorization for evidence; 6 is that correct? 7 A. Yes. 8 Q. Okay. And for the record, a Class 2B 9 recommendation is usefulness, efficacy, is less well 10 established by evidence opinion; is that right? 11 A. For 2B? 12 Q. Yeah. 13 A. Well, it's what we said. It may be 14 considered. Level B was going to be the randomized 15 control trial. Just to be complete, they also said 16 that patients with Lung Disease and severe 17 individualized approached treatment is recommended, 18 and that actually got a Class 1 recommendation, which 19 I certainly agree with. 20 Q. Do you agree with the use of the 2B 21 recommendation for inhaled treprostinil in patients 22 with PH associated with ILD as of 2022? 23 A. Yeah. I mean, absolutely. I think, you 24 know, whether you -- again, whether you say may be 25 considered or should be considered, you can debate</p>	<p style="text-align: right;">79</p> <p>1 following the rules. Class 1 or Class 2. It gets a 2 recommendation. It's not a Class 3 for sure. So 3 there's -- I would likely give it a Class 1 if I was 4 sitting on a committee. Yes. 5 Q. I think we can put that aside. I think 6 we've been going for about 50 minutes. Would now be 7 a good time for that break? 8 A. Sure. 9 VIDEOGRAPHER: We're going off the record 10 at 11:00 A.M. 11 (Recess taken.) 12 VIDEOGRAPHER: We're back on the record. 13 It's 11:16. 14 Q. Welcome back, Dr. Channick. If we could go 15 to Exhibit 1, which is your declaration, please. In 16 particular, I'd like to turn to paragraph 35. Sorry. 17 Not 35. I apologize. Paragraph 40, which is on 18 page 12. Are you there? 19 A. Yes. 20 Q. Okay. You say here, "physicians also 21 assess effectiveness of PH treatments using 22 hemodynamic parameters like the MPAP, PVR, and PAWP 23 measures I describe above." What is a hemodynamic 24 parameter? 25 A. A hemodynamic parameter is something you</p>
<p style="text-align: right;">78</p> <p>1 over the terminology, but certainly, you know, that's 2 correct. 3 Q. Why in your opinion, in the presence of the 4 data from the INCREASE trial, did inhaled 5 treprostinil for PHILD not receive a Class 1 6 recommendation? 7 A. Again, I think -- I don't know. Actually, 8 I don't know. I'm not going to speculate on what the 9 European experts decided about the grading system. 10 Q. Well, you said you agreed with the 2B 11 classification. So why would you not propose a 12 Class 1 for -- 13 A. I agreed with the Class 1 recommendation 14 that individualized treatment approach needs to be 15 taken in patients with ILD and Lung Disease and 16 severe PH, which is the fourth recommendation on this 17 table. That's absolutely what we should do is take 18 an individualized treatment approach. 19 Specifically your question about the 20 inhaled treprostinil and the 2B, I think, again, they 21 were following strict rules that we laid out already. 22 Q. So would you give inhaled treprostinil for 23 PHILD a Class 1 recommendation? 24 A. I probably would. I probably would based 25 on -- well, again, it depends on what you're</p>	<p style="text-align: right;">80</p> <p>1 measure. In this context, it's the pressure in the 2 pulmonary artery, for instance. The pulmonary 3 vascular resistance, the easiest way to explain that 4 is the resistance that the blood vessels in the lungs 5 give to the heart, the right side of the heart that 6 has to pump the blood through your lungs. So higher 7 pressure will usually mean a higher resistance. That 8 means the heart will have to work harder. It's a 9 measurement we can take to tell us really how severe 10 the Pulmonary Hypertension is in that respect. 11 Q. And that's distinct from a functional 12 measure like the six minute walk distance; is that 13 correct? 14 MR. SUKDUANG: Objection. Vague. 15 THE WITNESS: Well, it's a different test. 16 Yes. It's certainly not distinct, as we'll get into. 17 One, you know, affects the other for sure. 18 Q. In paragraph 39 above, you mentioned 19 another test called FVC or forced vital capacity. 20 What is FVC? 21 A. FVC is basically how much air a person can 22 breathe out when they take a breath all the way in, 23 fill up their lungs, and push it out as much as they 24 can. That amount of air that they're exhaling is the 25 force vital capacity.</p>

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<p>81</p> <p>1 Q. I think you just mentioned the hemodynamic 2 parameters can be correlated with exercise capacity. 3 Can FVC be correlated with exercise capacity as well? 4 A. Yeah. 5 Q. How so? 6 A. Well, I mean again, it's an indication of 7 Lung Disease, for instance, in a very general term. 8 So patients who have Lung Disease don't have a good 9 exercise capacity. 10 Q. Sure. So if a patient showed an 11 improvement if FVC after taking a particular 12 medication, would you expect them to exhibit enhanced 13 exercise capacity? 14 A. Not necessarily. It depends on degree. 15 Q. Okay. So let's go back to paragraph 40. 16 You say, "changes in hemodynamics are often 17 associated with changes in exercise capacity." 18 A. Yes. 19 Q. Do you provide any literature citations for 20 that sentence? 21 A. I mean, there's a deposition transcript 22 citation. 23 Q. Okay. 24 A. On there. 25 Q. Okay. So I think you're referring to the</p>	<p>83</p> <p>1 Q. Each of the citations you've pointed to in 2 footnote 22, they're all dated in 2022; is that 3 correct? 4 A. Yes. 5 Q. As a physician, do you typically review 6 deposition and trial transcripts? 7 A. I don't know what you mean by that. 8 Q. In your daily -- strike that. In your 9 daily practice of treating patients, do you have 10 occasion to read deposition and trial transcripts? 11 A. Not as part of treating patients, no. 12 Q. Would you make a prescribing decision based 13 on a deposition or trial transcript? 14 A. No. 15 Q. I believe you mentioned earlier today that 16 certain citations came from you and certain came from 17 counsel. Where did these come from in footnote 22? 18 A. Likely counsel. 19 Q. Okay. Dr. Channick, the court reporter's 20 handed you what's been marked as Exhibit 9. 21 (Exhibit 9 marked for identification.) 22 Q. This is a document bearing Bates Number 23 LIQ_PHILD_00000579 through 595. This is titled, 24 "deposition of Aaron Waxman MD, PHD, January 8th, 25 2022." Doctor, do you recognize Exhibit 9?</p>
<p>82</p> <p>1 next sentence with footnote 22; right? 2 A. Yeah. Yeah. That's correct. I apologize. 3 Q. Okay. So just for the sentence before that 4 you say, "changes in hemodynamics are often 5 associated with changes in exercise capacity." 6 There's no citation for that sentence; correct? 7 A. Correct. 8 Q. And then you say, "for example, a reduction 9 in PVR is generally correlated with improvements in 10 exercise capacity as measured by the 6MWD." Did I 11 get that right? 12 A. Yes. 13 Q. 6MWD is six-minute walk distance; right? 14 A. Yes. 15 Q. And then have you a citation here, footnote 16 22; correct? 17 A. Yes. 18 Q. Okay. Do you cite any literature or 19 scientific journal articles in footnote 22? 20 A. No. 21 Q. What do you cite in footnote 22? 22 A. Deposition transcript of Eric Waxman and 23 United Therapeutic Corporation versus Liquidia, 24 deposition transcript of Andrew Clark PHD, testimony 25 of Erin Waxman. Yeah. Those things.</p>	<p>84</p> <p>1 A. Yes. 2 Q. Is this the deposition transcript that's 3 cited in footnote 22 of your declaration? 4 A. Yes. 5 Q. Does this appear to be a complete copy of 6 the transcript of Dr. Waxman? 7 MR. SUKDUANG: The exhibit itself? 8 MR. ROMEO: Yeah. What I've handed to him. 9 MR. SUKDUANG: Did you give him a complete 10 copy? 11 MR. ROMEO: This is what you produced to 12 us. 13 MR. SUKDUANG: Oh. We didn't produce that. 14 You have it. 15 MR. ROMEO: It has your number on it. 16 MR. SUKDUANG: I know, but -- okay. So 17 you. 18 MR. ROMEO: Let me backup. I'll ask a 19 better question. I apologize. 20 Q. Do you see here in your citation of the 21 deposition transcript, refer to LIQPHILD five zeros 22 and then 79? 23 A. Five zeros and 79? Yes. 24 Q. Okay. So is Exhibit 9 the version of the 25 Waxman deposition transcript that you reviewed in</p>

Transcript of Richard Channick, M.D.

22 (85 to 88)

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<p>85</p> <p>1 preparing the declaration?</p> <p>2 A. I believe so.</p> <p>3 Q. Is this a complete version of the</p> <p>4 deposition transcript of Aaron Waxman?</p> <p>5 A. I don't know. It looks like it stops</p> <p>6 fairly abruptly. There's no sort of signatures and</p> <p>7 what not.</p> <p>8 Q. For example, you may notice it skips from</p> <p>9 page 8 to page 39.</p> <p>10 A. Okay.</p> <p>11 Q. Between pages 587 and 588.</p> <p>12 A. Correct.</p> <p>13 Q. Before you cited in your declaration did</p> <p>14 you ask counsel for a full copy of the transcript?</p> <p>15 A. No.</p> <p>16 Q. Okay. Did you review a full copy of the</p> <p>17 transcript?</p> <p>18 A. No.</p> <p>19 Q. Okay. Doctor, when you referred to</p> <p>20 particular deposition transcripts or trial</p> <p>21 transcripts, do you know if those were excerpted or</p> <p>22 full copies of those transcripts?</p> <p>23 MR. SUKDUANG: Objection. Vague.</p> <p>24 THE WITNESS: Yeah. I would have to look</p> <p>25 at specific ones to answer that.</p>	<p>87</p> <p>1 A. Not that I can recall.</p> <p>2 Q. Did you ask to review the opinions of</p> <p>3 Liquidia's prior experts?</p> <p>4 A. No.</p> <p>5 Q. Doctor, the court reporter's handed you</p> <p>6 what's been marked as Exhibit 10.</p> <p>7 (Exhibit 10 marked for identification.)</p> <p>8 Q. This is from the -- from case number</p> <p>9 20CV00755 in the United States District Court for the</p> <p>10 district of Delaware UTCV Liquidia rebuttal report of</p> <p>11 Dr. Nicholas Hill in response to the initial expert</p> <p>12 response of Dr. Aaron Waxman and Dr. Andrew Clark. I</p> <p>13 take it you have not seen Exhibit 10 before; is that</p> <p>14 correct?</p> <p>15 A. Correct.</p> <p>16 Q. But you did review portions of Dr. Waxman's</p> <p>17 expert report from this prior case; correct?</p> <p>18 A. Yes.</p> <p>19 Q. Are you familiar with Dr. Nicholas Hill?</p> <p>20 A. Yes.</p> <p>21 Q. Who is Dr. Nicholas Hill?</p> <p>22 A. He's a pulmonologist who is Pulmonary</p> <p>23 Hypertension specialist at Tufts University in</p> <p>24 Boston.</p> <p>25 Q. If you could turn to page 1, please. If</p>
<p>86</p> <p>1 MR. SUKDUANG: Are you asking was he</p> <p>2 provided full copies or what does he cite?</p> <p>3 MR. ROMEO: Well, thank you.</p> <p>4 Q. Did you review full copies of each of the</p> <p>5 transcripts that you've cited in your report?</p> <p>6 A. I honestly don't recall specifically. I</p> <p>7 would have to go back and look to be able to answer</p> <p>8 for each one.</p> <p>9 Q. Okay. Now, you're aware that -- strike</p> <p>10 that. All of the deposition transcripts and trial</p> <p>11 transcripts you've cited in footnote 22, those come</p> <p>12 from a prior litigation; correct? Not this</p> <p>13 litigation?</p> <p>14 A. Okay.</p> <p>15 Q. You understand that; right?</p> <p>16 A. Yes.</p> <p>17 Q. And you are aware that Dr. Waxman and Dr.</p> <p>18 Clark were experts for United Therapeutics; correct?</p> <p>19 A. Yes.</p> <p>20 Q. Okay. You understand that Liquidia in that</p> <p>21 litigation retained its own experts; correct?</p> <p>22 A. I would assume.</p> <p>23 Q. Have you reviewed any materials from</p> <p>24 Liquidia's experts in any prior litigation in</p> <p>25 offering your opinions in this case?</p>	<p>88</p> <p>1 you go to paragraph 1, do you see that Dr. Hill is</p> <p>2 submitting this rebuttal report on behalf of</p> <p>3 Liquidia?</p> <p>4 A. Yes.</p> <p>5 Q. Were you aware that Dr. Hill had been</p> <p>6 retained by Liquidia in the prior litigation?</p> <p>7 A. Yes.</p> <p>8 Q. Have you spoken with Dr. Hill regarding his</p> <p>9 work in the prior litigation?</p> <p>10 A. No.</p> <p>11 Q. And if you go to paragraph 4, please, it</p> <p>12 says, "my rebuttal expert report responds to the</p> <p>13 opinions represented in the initial expert reports of</p> <p>14 Dr. Aaron Waxman, Waxman report, and Dr. Andrew</p> <p>15 Clark, Clark report, both submitted by UTC on</p> <p>16 October 15, 2021, which I have reviewed." Did I get</p> <p>17 this right?</p> <p>18 A. Yes.</p> <p>19 Q. I believe you reviewed portions of at least</p> <p>20 one of those reports in preparing your declaration</p> <p>21 for this case?</p> <p>22 A. Yes.</p> <p>23 Q. Okay. And if you turn to page 42 of</p> <p>24 Exhibit 10, please.</p> <p>25 A. Okay.</p>

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<p>89</p> <p>1 Q. Do you see that Dr. Hill signed this</p> <p>2 November 12th, 2021?</p> <p>3 A. Yes.</p> <p>4 Q. Okay. Let's turn to page 23 of Dr. Hill's</p> <p>5 report, please. I'd like to direct your attention to</p> <p>6 paragraph 56, please. Actually, before we get there,</p> <p>7 let's go back to the first page. I'll come right</p> <p>8 back to 23?</p> <p>9 MR. SUKDUANG: Page 1?</p> <p>10 MR. ROMEO: Page 1, yes. Paragraph 1.</p> <p>11 Q. Do you see that Dr. Hill is submitting this</p> <p>12 rebuttal report in relation to U.S. patent number</p> <p>13 10716793 also known as the 793 patent?</p> <p>14 A. Yes.</p> <p>15 Q. Okay. And that was one of the references</p> <p>16 that you've analyzed as part of giving your opinions</p> <p>17 in this case?</p> <p>18 A. Yes.</p> <p>19 Q. Let's go back to page 23, paragraph 56.</p> <p>20 Dr. Hill says, "in contrast, for several reasons a</p> <p>21 POSA in a 2006 and today would have understood that</p> <p>22 changes in hemodynamic values may not correlate with</p> <p>23 therapeutic effectiveness." Do you see that?</p> <p>24 A. Yes.</p> <p>25 Q. Do you agree or disagree with Dr. Hill in</p>	<p>91</p> <p>1 Q. So if you could turn to the next page, I'd</p> <p>2 like to go to the end of this paragraph. Dr. Hill</p> <p>3 writes, "accordingly, POSA as of May 2006 would have</p> <p>4 understood that for a Pulmonary Hypertension</p> <p>5 treatment to be, quote, therapeutically effective,</p> <p>6 end quote, one would need to assess primary end</p> <p>7 points such as improvement in breathing on exertion,</p> <p>8 exercise capacity measured by the 6MWT, improvement</p> <p>9 in the NYHA functional classification, QOL scores,</p> <p>10 and survival." Do you see that?</p> <p>11 A. Yes.</p> <p>12 Q. Do you agree or disagree with that</p> <p>13 statement?</p> <p>14 A. I think I disagree with it. I would say it</p> <p>15 depends on what you are talking about. We've kind of</p> <p>16 alluded to this. To get FDA approval, one would</p> <p>17 typically need to show a measure of what we call,</p> <p>18 feels, functions, and survives. When you start</p> <p>19 talking about things like POSA, then you're talking</p> <p>20 about patents and what not, and that is not required.</p> <p>21 So if we're talking about -- you have to be</p> <p>22 very specific, are you talking about effective to get</p> <p>23 FDA approval or effective to get a patent, for</p> <p>24 instance? We don't use the term POSA when we're</p> <p>25 talking about FDAs and that. So if you'd be more</p>
<p>90</p> <p>1 this context?</p> <p>2 A. I disagree.</p> <p>3 Q. How so?</p> <p>4 A. I think we have a lot of data and</p> <p>5 experience that hemodynamic changes do correlate with</p> <p>6 effectiveness in exercise capacity. We have studies</p> <p>7 even with treprostinil, for instance, showing</p> <p>8 six-minute walk distance improvements. We also know</p> <p>9 that -- I'm sure we'll talk about these papers, but</p> <p>10 there's plenty of evidence, and we know that</p> <p>11 hemodynamics is what Pulmonary Hypertension is.</p> <p>12 Not to get too pedantic, but this is a</p> <p>13 disease of high pressure and resistance, and drugs</p> <p>14 work for Pulmonary Hypertension by reducing that</p> <p>15 pressure and resistance. That's how pulmonary</p> <p>16 vasodilators work. They don't work on the brain.</p> <p>17 They don't work on the muscles. I think everybody</p> <p>18 would agree to that. So the only reason they work is</p> <p>19 because they improve the hemodynamics. That means</p> <p>20 that they then will lead to improved function in how</p> <p>21 patients feel and how they walk. This is not</p> <p>22 debated. This is how the drugs work. Does it always</p> <p>23 correlate? No. Obviously, nothing is 100 percent.</p> <p>24 Very fundamentally, hemodynamic improvements are</p> <p>25 necessary to get clinical improvements.</p>	<p>92</p> <p>1 specific as to which of those two things you're</p> <p>2 talking about I can answer better.</p> <p>3 Q. Okay. So you've reviewed the 793 patent in</p> <p>4 connection with your opinions in this case; right?</p> <p>5 A. Yes.</p> <p>6 Q. Okay. And we'll look at that a little bit</p> <p>7 later today. Here, Dr. Hill is talking about</p> <p>8 therapeutically effective, that term in the context</p> <p>9 of the 793 patent which you've reviewed. So do you</p> <p>10 agree that for a person of ordinary skill to assess</p> <p>11 whether a Pulmonary Hypertension would be</p> <p>12 therapeutically effective for purposes of the 793</p> <p>13 patent, they would need to assess primary end points</p> <p>14 such as improvement on breathing on exertion,</p> <p>15 exercise capacity measured by the six-minute walk</p> <p>16 test, improvement in NYHA functional classification,</p> <p>17 QOL scores, and survival?</p> <p>18 MR. SUKDUANG: Objection. Calls for a</p> <p>19 legal conclusion regarding infringement.</p> <p>20 THE WITNESS: You would -- okay. If we're</p> <p>21 going to get into the 793 patent, there would have to</p> <p>22 be evidence of -- as there is, which we'll get into,</p> <p>23 of the drugs having effects on exercise capacity,</p> <p>24 functional class, and, again, I don't know how deep</p> <p>25 you want to get into this. I don't know exactly what</p>

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<p>93</p> <p>1 he means by therapeutically effective in this</p> <p>2 particular statement. But we certainly -- there's</p> <p>3 certainly plenty of evidence that that's present,</p> <p>4 that we can go through.</p> <p>5 Q. Okay. So in the context of the 793 patent,</p> <p>6 do you agree or disagree with Dr. Hill's statement?</p> <p>7 MR. SUKDUANG: Objection. Vague.</p> <p>8 Objection to the extent it calls for a legal</p> <p>9 conclusion on the issue of infringement.</p> <p>10 THE WITNESS: Yeah. I guess I'm having a</p> <p>11 little -- I'm not a lawyer, so I'm having a little</p> <p>12 trouble. We have to be very specific. Are we</p> <p>13 talking about a medical point of view? A patent</p> <p>14 point of view?</p> <p>15 Q. Sure. Doctor, the court reporter's handed</p> <p>16 you what's been marked as Exhibit 11, which is U.S.</p> <p>17 patent number 10 -- strike that. 10716793.</p> <p>18 (Exhibit 11 marked for identification.)</p> <p>19 Q. Doctor, are you familiar with Exhibit 11?</p> <p>20 A. Yes.</p> <p>21 Q. What is Exhibit 11?</p> <p>22 A. That's the patent that you just said. 793.</p> <p>23 Q. Okay. And you've analyzed this patent in</p> <p>24 connection with giving your opinions in this case?</p> <p>25 A. Yes.</p>	<p>95</p> <p>1 that gets it, or some patients?</p> <p>2 Q. Okay. Let's do both. Would each and every</p> <p>3 ILD patient to which -- strike that. If you perform</p> <p>4 the methods that are claimed in 793, will each and</p> <p>5 every ILD patient improve exercise capacity, in your</p> <p>6 opinion?</p> <p>7 A. No.</p> <p>8 Q. Why not?</p> <p>9 A. Because nothing works for everybody. We</p> <p>10 know that in real life in diseases that some patients</p> <p>11 benefit more than others.</p> <p>12 Q. And in fact, that was seen in the INCREASE</p> <p>13 trial where not every patient received a benefit;</p> <p>14 correct?</p> <p>15 A. Correct.</p> <p>16 Q. Now, you said, patients generally. So if</p> <p>17 performing the method claimed in 793 on PHILD</p> <p>18 patients, in your expert opinion, what proportion of</p> <p>19 PHILD patients would show an improvement in exercise</p> <p>20 capacity?</p> <p>21 A. More than 50 percent. It's not just my</p> <p>22 opinion, of course. It's prior studies that were</p> <p>23 published at the time, we can review that are in my</p> <p>24 declaration, Agarwal and Saggar. I'm happy to go</p> <p>25 through those.</p>
<p>94</p> <p>1 Q. And you've analyzed both the specification</p> <p>2 -- strike that. If you turn to the last page, column</p> <p>3 18, do you see that the claims are listed at the end</p> <p>4 of column 18?</p> <p>5 A. Yes.</p> <p>6 Q. And you've analyzed the claims of the 793</p> <p>7 patent in connection with your opinions in this case;</p> <p>8 correct?</p> <p>9 A. Yes.</p> <p>10 Q. Okay. Correct me if I'm wrong, is it your</p> <p>11 opinion that a person of -- strike that. If a person</p> <p>12 were to perform the method that's described in these</p> <p>13 claims in a PHILD patient, they would improve</p> <p>14 exercise capacity?</p> <p>15 A. Yes.</p> <p>16 Q. Okay. Let's look at the first one of those</p> <p>17 claims.</p> <p>18 A. You're not talking about every patient;</p> <p>19 right?</p> <p>20 Q. Well, let's break that down. So why the</p> <p>21 need for the caveat?</p> <p>22 A. Well, because you said a patient. I don't</p> <p>23 want to make a universal statement.</p> <p>24 Q. Okay.</p> <p>25 A. Are you referring to each and every patient</p>	<p>96</p> <p>1 Q. I promise we will go through those.</p> <p>2 A. I'm sure we will.</p> <p>3 Q. I want to look at claim 1 of the 793</p> <p>4 patent. It reads, "a method of treating Pulmonary</p> <p>5 Hypertension comprising administering by inhalation</p> <p>6 to a human suffering from Pulmonary Hypertension, a</p> <p>7 therapeutically effective single event dose of a</p> <p>8 formulation comprising treprostinil or a</p> <p>9 pharmaceutically acceptable salt thereof, with an</p> <p>10 inhalation device wherein the therapeutically</p> <p>11 effective single event dose comprises from 15</p> <p>12 micrograms to 90 micrograms of treprostinil, or a</p> <p>13 pharmaceutically acceptable salt thereof delivered in</p> <p>14 one to three breaths."</p> <p>15 Did I get that right?</p> <p>16 A. Yes.</p> <p>17 Q. Okay. Do you see that twice in claim 1</p> <p>18 there's a reference to therapeutically effective</p> <p>19 single event dose?</p> <p>20 A. Yes.</p> <p>21 Q. When you analyze the claims of the 793</p> <p>22 patent for purposes of giving your opinions in this</p> <p>23 case, what meaning did you ascribe to</p> <p>24 "therapeutically effective single event dose"?</p> <p>25 A. They're describing a treatment, a dose that</p>

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<p style="text-align: right;">97</p> <p>1 one would get of this medication. They're describing</p> <p>2 the method for delivering that dose, and the dose of</p> <p>3 that dose in this claim.</p> <p>4 Q. Okay. And what meaning particularly did</p> <p>5 you ascribe to the phrase, "therapeutically</p> <p>6 effective"?</p> <p>7 MR. SUKDUANG: Objection to the extent</p> <p>8 you're calling for a legal conclusion on claim</p> <p>9 construction.</p> <p>10 THE WITNESS: I don't know that I ascribed</p> <p>11 a specific meaning other than what it says. It's</p> <p>12 effective.</p> <p>13 Q. In your analysis of this claim, did you</p> <p>14 interpret "therapeutically effective" to include an</p> <p>15 increase in exercise capacity?</p> <p>16 A. I did.</p> <p>17 Q. In your interpretation of this claim for</p> <p>18 purposes of your opinions in this case, did you</p> <p>19 interpret "therapeutically effective" as requiring an</p> <p>20 increase in exercise capacity?</p> <p>21 A. No.</p> <p>22 Q. Can you explain?</p> <p>23 A. Because there are other things that</p> <p>24 constitute effectiveness than exercise capacity of a</p> <p>25 therapy like this.</p>	<p style="text-align: right;">99</p> <p>1 Q. This is a review article entitled, "the</p> <p>2 changing paradigm in Pulmonary Hypertension trials,</p> <p>3 longer duration, new endpoints." Published in</p> <p>4 current opinion in pulmonary medicine in 2015.</p> <p>5 Doctor, do you recognize Exhibit 12?</p> <p>6 A. Yes.</p> <p>7 Q. What is it?</p> <p>8 A. It's an article that I wrote with another</p> <p>9 physician on the title that you read.</p> <p>10 Q. And for those of us who are not as steeped</p> <p>11 in clinical trial design as you are, what's an</p> <p>12 endpoint?</p> <p>13 A. An endpoint is a measurement that you take</p> <p>14 when you test, in this case, a medication. It's what</p> <p>15 you're measuring to look at the effect of the</p> <p>16 medication.</p> <p>17 Q. And have you heard of both a primary and a</p> <p>18 secondary endpoint?</p> <p>19 A. Yes.</p> <p>20 Q. And what's the difference between a primary</p> <p>21 and a secondary endpoint?</p> <p>22 A. Well, methodologically and statistically,</p> <p>23 when you're doing a study design -- again, I'm going</p> <p>24 to get into the weeds a little bit. The primary</p> <p>25 endpoint is what you do -- you do what's called a</p>
<p style="text-align: right;">98</p> <p>1 Q. So when you interpreted therapeutically</p> <p>2 effective for purposes of your opinion in this case,</p> <p>3 you said therapeutically effective could include an</p> <p>4 increase in exercise capacity, but not necessarily;</p> <p>5 is that right?</p> <p>6 MR. SUKDUANG: Objection. Vague. Calls</p> <p>7 for a claim construction. Excuse me. Objection.</p> <p>8 Vague. And objection for a legal conclusion to the</p> <p>9 extent you're asking for a claim construction.</p> <p>10 THE WITNESS: Yes.</p> <p>11 Q. Okay. Now, doctor, did you review the</p> <p>12 entirety of the 793 patent in connection with giving</p> <p>13 your opinions in this case?</p> <p>14 A. Yes.</p> <p>15 Q. Does the phrase "exercise capacity" appear</p> <p>16 anywhere in the 793 patent?</p> <p>17 A. No.</p> <p>18 Q. Does the phrase "exercise ability" appear</p> <p>19 anywhere in the 793 patent?</p> <p>20 A. No.</p> <p>21 Q. All right. You can put that aside for now.</p> <p>22 We'll come back to it. I promise.</p> <p>23 Dr. Channick, the court reporter's handed</p> <p>24 you what's been marked Exhibit 12.</p> <p>25 (Exhibit 12 marked for identification.)</p>	<p style="text-align: right;">100</p> <p>1 power analysis. That's the first thing you're</p> <p>2 looking at. So when you design the study to</p> <p>3 determine, for instance, how many patients you need</p> <p>4 to put in, you do it around the primary endpoint of</p> <p>5 the study.</p> <p>6 So it's a way to methodologically design a</p> <p>7 study. What endpoint you use as a primary endpoint</p> <p>8 is a much more complex question that we can delve</p> <p>9 into if you would like.</p> <p>10 Q. And in your experience, what's the most</p> <p>11 common primary endpoint for Pulmonary Hypertension</p> <p>12 trials?</p> <p>13 MR. SUKDUANG: Objection. Vague.</p> <p>14 THE WITNESS: Yeah. It's hard to say. I</p> <p>15 think for -- as I said, registration trials, and now</p> <p>16 we're talking FDA, so very distinct, they typically</p> <p>17 require a primary endpoint of how a patient feels,</p> <p>18 functions, or survives. So how they feel would be</p> <p>19 something like the functional class or symptoms.</p> <p>20 Functions could be exercise capacity. Survives is</p> <p>21 survival.</p> <p>22 So those would often be the primary</p> <p>23 endpoints in registration trials, like phase 3</p> <p>24 studies. In phase 2 studies, we're often using</p> <p>25 things like hemodynamic endpoints that won't get the</p>

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<p style="text-align: right;">101</p> <p>1 drug FDA approved, but they're very important to see</p> <p>2 a hemodynamic effect. Long answer. Sorry.</p> <p>3 Q. That's okay. All right. If you look at</p> <p>4 the first page of your review article under purpose</p> <p>5 of review, it says, "approved therapies for pulmonary</p> <p>6 arterial hypertension currently consists of 12</p> <p>7 agents, the majority of which were approved following</p> <p>8 short-term randomized clinical trials using change in</p> <p>9 six-minute walk distance, 6MWD, as the primary</p> <p>10 outcome"; is that right?</p> <p>11 A. Yes.</p> <p>12 Q. Okay. And what is the six-minute walk</p> <p>13 distance test?</p> <p>14 A. So it's a really simple test. You</p> <p>15 basically have a hallway and you measure the distance</p> <p>16 a patient walks up and down that hallway in</p> <p>17 6 minutes.</p> <p>18 Q. Okay. And why is 6-minute walk distance --</p> <p>19 why was that used, to your knowledge, as the primary</p> <p>20 endpoint for the majority of the trials for PIH that</p> <p>21 you looked at here?</p> <p>22 A. I mean, I wasn't involved in all of these</p> <p>23 trials in development. I would be speculating. It</p> <p>24 is a test that seems to correlate well with outcomes</p> <p>25 and other parameters. It's certainly an easy to do</p>	<p style="text-align: right;">103</p> <p>1 can walk.</p> <p>2 Q. Sure. What type of endpoint is FEC in the</p> <p>3 context of PHILD?</p> <p>4 A. FEC would be a surrogate endpoint. It's</p> <p>5 actually probably not a surrogate endpoint because</p> <p>6 it's really not shown to correlate with outcomes,</p> <p>7 necessarily. So it's a -- it would be typically a</p> <p>8 secondary endpoint. Whether it's a true surrogate</p> <p>9 endpoint, it probably isn't, actually.</p> <p>10 Q. Okay. And hemodynamics would be a</p> <p>11 surrogate endpoint?</p> <p>12 A. Yes, I think there's pretty good evidence</p> <p>13 that hemodynamics are surrogate endpoints. And that</p> <p>14 gets to my previous points that changes in</p> <p>15 hemodynamics likely correlate with improvements in</p> <p>16 clinical parameters.</p> <p>17 Q. Okay. I want to go to the last sentence of</p> <p>18 the -- surrogate endpoints at the paragraph. The</p> <p>19 paragraph continues into the next column, and I want</p> <p>20 to look at the last sentence in that paragraph. It</p> <p>21 says, "in addition, the appropriateness of use of</p> <p>22 hemodynamic measures as surrogates has been</p> <p>23 questioned with some data suggesting that changes in</p> <p>24 hemodynamics are not true mediators of the</p> <p>25 relationship between treatment and clinical</p>
<p style="text-align: right;">102</p> <p>1 study. When you're designing a large trial, you</p> <p>2 don't want something super difficult for an</p> <p>3 investigator to do. All you need is a hallway, a</p> <p>4 stopwatch and a tape measure.</p> <p>5 Q. Sure. If you could turn to page 443 in</p> <p>6 your review article, please. Do you see there's a</p> <p>7 heading that says, "surrogate endpoint"?</p> <p>8 A. Yes.</p> <p>9 Q. Okay. And by a "surrogate endpoint", that</p> <p>10 would be a type of secondary endpoint; right?</p> <p>11 A. It is a secondary endpoint, typically.</p> <p>12 Well, no. Let me correct that. I misspoke. A</p> <p>13 surrogate endpoint can be a primary endpoint. A</p> <p>14 surrogate endpoint is something that should correlate</p> <p>15 with the feels, functions, or survives measurement.</p> <p>16 And so, you know, things like -- and it can be a</p> <p>17 primary endpoint. It's just that it correlates with</p> <p>18 a feels, functions, survive endpoint, typically.</p> <p>19 Q. So is the six-minute walk test a surrogate</p> <p>20 endpoint or a direct endpoint?</p> <p>21 A. That's a great question. It's actually</p> <p>22 something we debate in our -- it's probably somewhat</p> <p>23 both. Because it may be a surrogate income for other</p> <p>24 outcomes like survival, but it also can be a</p> <p>25 clinically important endpoint. Like how far someone</p>	<p style="text-align: right;">104</p> <p>1 outcomes." Did I read that correctly?</p> <p>2 A. Yes.</p> <p>3 Q. What are you referring to there?</p> <p>4 A. Show me where that is, again. I'm sorry.</p> <p>5 Q. Sure. It's the last sentence of the first</p> <p>6 paragraph under surrogate endpoints.</p> <p>7 A. Got it. Okay. Again, I'd have to go way</p> <p>8 back to look. I think we're trying to make the point</p> <p>9 that nothing's 100 percent, and there are certainly</p> <p>10 cases where -- some studies where hemodynamics didn't</p> <p>11 correlate as well as others. We're talking</p> <p>12 methodology here. We're not talking about individual</p> <p>13 patients.</p> <p>14 Again, this was almost ten years ago. I</p> <p>15 don't recall exactly what we were referring to. I</p> <p>16 think we were just trying to put some balance into</p> <p>17 the paper to suggest that, you know, you still need</p> <p>18 -- you know, nothing's 100 percent. I mean, that's</p> <p>19 all I can say. I'm speculating on what we meant more</p> <p>20 than that.</p> <p>21 Q. Okay. I think you can put that aside.</p> <p>22 A. Just to finish so everybody knows. It</p> <p>23 looks like in that one reference I gave, it had more</p> <p>24 to do with clinical worsening events. So changes in</p> <p>25 the hemodynamics in the clinical worsening didn't</p>

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<p style="text-align: right;">105</p> <p>1 talk about exercise capacity in that reference 50</p> <p>2 that we referred to in that. So it's a little bit</p> <p>3 apples and oranges from what we're talking about, but</p> <p>4 -- anyway.</p> <p>5 Q. Dr. Channick, the court reporter's handed</p> <p>6 you what's been marked Exhibit 13.</p> <p>7 (Exhibit 13 marked for identification.)</p> <p>8 Q. This is another composite document</p> <p>9 consisting of the transcript and a cover page for a</p> <p>10 YouTube video entitled, "managing pulmonary arterial</p> <p>11 hypertension therapeutic selection and coordination</p> <p>12 from the PCMH Congress, September 14th to 16, 2018,</p> <p>13 in San Diego." Did you attend a PCMH Congress in San</p> <p>14 Diego in 2018?</p> <p>15 A. Apparently, I did. I attend a lot of</p> <p>16 Congress. If you asked me what it stood for, I</p> <p>17 couldn't even tell you.</p> <p>18 Q. That's fair enough. Again, this is like</p> <p>19 the last exhibit. We've provided the YouTube URL</p> <p>20 here. I'll note for the record, this was posted to</p> <p>21 YouTube, at least by our measure, on March 21, 2019,</p> <p>22 but the URL was provided on the first page.</p> <p>23 If we go to the transcript, let's go to</p> <p>24 page 2. Do you see here starting on line 2 you say,</p> <p>25 "I'm Dr. Richard Channick. I'm a pulmonologist at</p>	<p style="text-align: right;">107</p> <p>1 A. Well, we may treat different causes</p> <p>2 different ways. It's pretty self-- do you want me</p> <p>3 to be specific?</p> <p>4 Q. Sure.</p> <p>5 A. And go through all the causes of Pulmonary</p> <p>6 Hypertension and how you would treat them. I'm happy</p> <p>7 to do that.</p> <p>8 Q. No. It's okay. I think I understand your</p> <p>9 point. If we go to the next page, page 4 starting at</p> <p>10 17. Page 19. You say --</p> <p>11 MR. SUKDUANG: Sorry. Page 19?</p> <p>12 MR. ROMEO: Sorry. I apologize, counsel.</p> <p>13 Let's go to page 4, line 17.</p> <p>14 Q. You say, "and again, I would underscore" --</p> <p>15 I think it's supposed to be underscore. "The</p> <p>16 Pulmonary Hypertension isn't one disease. In fact,</p> <p>17 it isn't even a disease, it's a number. Its elevated</p> <p>18 blood pressure in the lungs due to one of these</p> <p>19 conditions."</p> <p>20 MR. SUKDUANG: I'm sorry. You misstated</p> <p>21 and you said you believed it should say underscore.</p> <p>22 It literally says understand. So is this transcript</p> <p>23 incorrect?</p> <p>24 MR. ROMEO: I understand it to be</p> <p>25 certified.</p>
<p style="text-align: right;">106</p> <p>1 UCLA Medical Center as of two weeks ago, so I drove</p> <p>2 down here. Which is nice. I was in Boston for many</p> <p>3 years at MASS general doing sort of the same thing,</p> <p>4 Pulmonary Hypertension." Did I get that right?</p> <p>5 A. Yes.</p> <p>6 Q. Does this refresh your recollection as to</p> <p>7 your attendance at this conference?</p> <p>8 A. No. I mean, I certainly speak at many,</p> <p>9 many conferences. This particular one in San Diego</p> <p>10 --</p> <p>11 Q. Okay. So if you could turn to page 3 of</p> <p>12 the transcript here. Starting around line 10 you</p> <p>13 say, "so when we talk about Pulmonary Hypertension,</p> <p>14 you need to understand we're talking about -- we're</p> <p>15 not talking about one condition or one disease.</p> <p>16 We're talking about a bunch of conditions and</p> <p>17 diseases, and this is really critical because how we</p> <p>18 treat Pulmonary Hypertension depends completely on</p> <p>19 what's causing it." Did I get that right?</p> <p>20 A. Yes.</p> <p>21 Q. Do you agree with that statement?</p> <p>22 A. Yes.</p> <p>23 Q. How does the treatment of Pulmonary</p> <p>24 Hypertension relate to the cause of the Pulmonary</p> <p>25 Hypertension?</p>	<p style="text-align: right;">108</p> <p>1 MR. SUKDUANG: Well now I call into</p> <p>2 question the veracity of the transcript.</p> <p>3 MR. ROMEO: You can do that.</p> <p>4 Q. It reads, "and again, I would understand</p> <p>5 the point, the Pulmonary Hypertension isn't even a</p> <p>6 disease, it's a number. It's elevated blood pressure</p> <p>7 in the lungs due to one of these conditions." Did I</p> <p>8 read that correctly?</p> <p>9 A. Yes.</p> <p>10 Q. Okay. And I believe you mentioned this</p> <p>11 earlier. Could you explain why Pulmonary</p> <p>12 Hypertension is a number, not a disease in your</p> <p>13 opinion?</p> <p>14 A. Because that's what it is. Hypertension</p> <p>15 means elevated pressure. Pulmonary means lung. So</p> <p>16 lung elevated pressure.</p> <p>17 Q. Okay. I won't read it all into the record</p> <p>18 here, but if you go to the next paragraph which</p> <p>19 begins on line 22 of page 4 and continues onto</p> <p>20 page 5, do you see that you generally discussed group</p> <p>21 1 Pulmonary Hypertension, or PAH?</p> <p>22 A. Yes.</p> <p>23 MR. SUKDUANG: Excuse me. Give me an</p> <p>24 opportunity. Mischaracterizes, because the paragraph</p> <p>25 goes on for several pages. So I'm going to object as</p>

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<p style="text-align: right;">109</p> <p>1 mischaracterizing with respect to only group 1. He 2 can keep going. 3 THE WITNESS: You have to say it again. 4 Q. I'll start again. Do you see that at 5 line 13 there's a reference to connective tissue 6 disease? 7 A. Yes. 8 Q. Okay. Are you stating here that connective 9 tissue disease is a group 1 condition or something 10 else? 11 MR. SUKDUANG: You can read what you need 12 to understand and answer the question. 13 THE WITNESS: This is likely to a lay 14 audience. We're trying to be very simple and basic, 15 which is fine. 16 Q. Okay. 17 A. I'm not speaking to a bunch of experts in 18 this talk, I guarantee it. So yes, connective tissue 19 diseases, HIV, if you see the sentence there, fall 20 within group one. In this context, that's my 21 interpretation of what I said. 22 Q. Can connective tissue disease exist in 23 other groups of PH as well? 24 A. Yes. 25 Q. How so?</p>	<p style="text-align: right;">111</p> <p>1 So if you treat a patient effectively, those 2 pressures will come down. The resistance in those 3 arteries will come down as well, but in Pulmonary 4 Hypertension drugs, you'll never get approved based 5 on their ability to lower the pressure. You have to 6 have some sort of functional outcome or measure. 7 What we say in the reg, in the regulatory 8 field, is that the drug either has to improve how a 9 patient feels, functions, or survives. That's the 10 mantra for Pulmonary Hypertension." Did I get that 11 right. 12 A. Yes. 13 Q. Is that a correct statement when you made 14 it in 2018? 15 A. Yeah. I mean, it's still a correct 16 statement. We're talking about FDA approval, 17 regulatory approval, of a drug. That's the feels, 18 functions, and survives mantra. 19 Q. And then line 12 you say, "the other thing, 20 though, that we know is that how much each drug 21 improves a specific patient is very variable. In 22 spite having done this for 30 years, I can still not 23 predict in a given patient how they're going to 24 respond to a given therapy." Did I get that right? 25 A. Yes.</p>
<p style="text-align: right;">110</p> <p>1 A. Because patients with connective tissue 2 diseases can develop ILD. And if we think those 3 patients have ILD and PH, we may call it group 3. 4 Patients with connective tissue diseases can develop 5 Heart Disease, or left-sided heart disease, in which 6 case we might classify them in group 2. That type of 7 thing. 8 Q. Let's turn to page 15 of the transcript, 9 please. Let's start at line 11. It says here, "the 10 vast majority, in fact all except one now, is 11 actually two because of a recent approval, but have 12 been approved with that one specific primary 13 endpoint, and that was the ability of the drug to 14 improve exercise capacity as measured by a six-minute 15 walk test. 16 So that was the primary endpoint that led 17 to approval. It's not showing an improvement in 18 mortality. It's not showing other endpoints but it's 19 improving exercise capacity and that's really been 20 how the drugs have been studied and how we designed 21 this trial early on." 22 Did I get that right? 23 A. Yes. 24 Q. If you go to the next page, 16, you say, 25 "now, these therapies do improve the hemodynamics.</p>	<p style="text-align: right;">112</p> <p>1 Q. Was that a true statement in 2018 and 2 today? 3 A. Yes, the patients don't all respond the 4 same way to medications. 5 Q. We can put that aside. Let's go to 6 Exhibit 2 which we looked at a little earlier today. 7 This again is the letter to the editor in response to 8 the INCREASE study; is that correct? 9 A. Yes. 10 Q. Okay. And this later begins on page 1870; 11 right? 12 A. Yes. 13 Q. The third sentence of this letter states, 14 "the extent of Interstitial Lung Disease is the key 15 distinguishing feature between pulmonary arterial 16 hypertension and group 3 pulmonary hypertension. 17 Therefore, verifying the extent of interstitial lung 18 disease is crucial, particularly since mild 19 Interstitial Lung was routinely included in previous 20 studies of pulmonary arterial hypertension." Did I 21 get that right? 22 A. Yes. 23 Q. So why is verifying the extent of 24 interstitial lung disease crucial when studying 25 PHILD?</p>

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<p style="text-align: right;">113</p> <p>1 A. Well, the more information you can get on 2 who the patients are that were in the study, the more 3 useful you can use the results of that study. To put 4 it another way, again, we talk about this group 3 5 versus group 1 distinction and how muddy it is. So 6 if you were to study patients in a trial that had -- 7 that all had very severe interstitial lung disease 8 and very mild Pulmonary Hypertension versus studying 9 patients in a trial that had very mild interstitial 10 lung disease and very severe Pulmonary Hypertension, 11 that would be important to know. So the point we 12 were trying to make is that -- characterizing the 13 patients in as much detail as possible is really 14 helpful.</p> <p>15 Q. Now, there's a reference in the two 16 sentences I just read to you that refers to mild 17 interstitial lung disease being routinely included in 18 previous studies of pulmonary arterial hypertension. 19 Would you consider a patient with PH that has mild 20 interstitial lung disease to be a PHILD patient?</p> <p>21 A. It depends on the patient and whether we 22 could have found other risk factors for PAH. I mean, 23 I think that at the extremes it's kind of easy. Let 24 me try to keep it simple here. If you had a patient 25 with just a tiny bit of fibrosis, they had like, one</p>	<p style="text-align: right;">115</p> <p>1 A. Okay.</p> <p>2 Q. Do you see that the claims are listed?</p> <p>3 A. Yes.</p> <p>4 Q. Okay. Claim 1 begins, "a method of 5 improving exercise capacity in a patient having 6 Pulmonary Hypertension associated with interstitial 7 lung disease", and it goes on from there. In 8 offering your opinions on the validity and 9 infringement of these claims, what meaning did you 10 assign to Pulmonary Hypertension associated with 11 interstitial lung disease?</p> <p>12 MR. SUKDUANG: Objection to the extent it 13 calls for a legal conclusion.</p> <p>14 THE WITNESS: I don't understand what you 15 mean by what meaning I ascribed. I mean, it's pretty 16 self-explanatory.</p> <p>17 Q. Okay. Today we've talked a little about 18 the muddiness between group 1 and group 3 patients. 19 So when you conducted your analysis of this patent, 20 where did you draw the line in terms of determining 21 whether a particular patient had PHILD versus not?</p> <p>22 A. I think it's what the patient is diagnosed 23 with. I don't know that I did the analysis the way 24 that you are describing. I think if a physician 25 makes a diagnosis of Pulmonary Hypertension</p>
<p style="text-align: right;">114</p> <p>1 or two little scars on their x-ray, but they had 2 very, very severe Pulmonary Hypertension, and it was 3 maybe somebody who fit profile of Idiopathic PAH, 4 like a young woman with no other risk factors, I 5 would probably call that group one, and in fact, 6 those patients were included in group one studies 7 that lead to approval of all these drugs.</p> <p>8 At the other extreme, again, it's pretty 9 easy too. We still debate that middle ground. I 10 can't give you like a set criteria for this patient, 11 it's group 3, for this patient, it's group 1. It's 12 just not -- it's a limitation of the classification 13 system, as I'm sure you're learning.</p> <p>14 Q. Yes. Okay. The court reporter's handed 15 you what's been marked as Exhibit 14.</p> <p>16 (Exhibit 14 marked for identification.)</p> <p>17 Q. This is U.S. patent number 11826327. Do 18 you recognize Exhibit 14, doctor?</p> <p>19 A. Yes.</p> <p>20 Q. Is this the patent that you analyzed for 21 both infringement and validity in your declaration in 22 this case?</p> <p>23 A. Yes.</p> <p>24 Q. Let's turn to the -- turn to column 54, the 25 second to last page.</p>	<p style="text-align: right;">116</p> <p>1 associated with ILD, that's the diagnosis. It's a 2 clinician's diagnosis. So I don't -- that's pretty 3 much all I can say.</p> <p>4 Q. Okay. That's fair. I think we've been 5 going for a little bit over an hour now. Is now a 6 good time for a lunch break?</p> <p>7 MR. SUKDUANG: I'm not trying to ask you to 8 do work, but could you go check if lunch is there?</p> <p>9 MR. BURROWBRIDGE: Want to go off the 10 record.</p> <p>11 VIDEOGRAPHER: We're going off the record. 12 The time is 12:12.</p> <p>13 (Lunch taken.)</p> <p>14 VIDEOGRAPHER: We're back on the record. 15 It's 12:57 P.M.</p> <p>16 Q. Welcome back, Dr. Channick. During the 17 break, did you speak with counsel about the substance 18 of your testimony?</p> <p>19 A. No.</p> <p>20 Q. Doctor, if you could pull out Exhibit 11, 21 which is the 793 patent, please.</p> <p>22 A. Okay.</p> <p>23 Q. In particular, I'd like to go to Table 2 24 which is on column 11?</p> <p>25 A. Okay.</p>

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<p>117</p> <p>1 Q. Did you review Table 2 in offering your</p> <p>2 opinions in this case?</p> <p>3 A. Yes.</p> <p>4 Q. What do you understand Table 2 to describe?</p> <p>5 A. It describes hemodynamic effects of</p> <p>6 different doses of inhaled treprostinil.</p> <p>7 Q. Okay. And approximately how many patients</p> <p>8 were involved in this study?</p> <p>9 A. Well, if we add up the columns we see</p> <p>10 there's about 12, 9, and 20, plus placebo.</p> <p>11 Q. That would be about 45?</p> <p>12 A. About 45.</p> <p>13 Q. Okay. Of which 4 were placebo; right?</p> <p>14 A. Yes.</p> <p>15 Q. Okay. And I believe if you look back to</p> <p>16 column 8, this is part of example 1 of the 793</p> <p>17 patent; is that right?</p> <p>18 A. Yes.</p> <p>19 Q. Okay. And example 1 is an open label study</p> <p>20 upon acute safety, tolerability, and hemodynamic</p> <p>21 effects of inhaled treprostinil delivered in seconds;</p> <p>22 right?</p> <p>23 A. Yes.</p> <p>24 Q. Okay. And if you go to table -- strike</p> <p>25 that. Column 9, line 36. Please. It says, "a total</p>	<p>119</p> <p>1 Q. Okay. So if we return to Table 2 on column</p> <p>2 11, does the 793 patent tell you which disease</p> <p>3 etiology -- strike that. Does the 793 patent tell</p> <p>4 you where those four pulmonary fibrosis patients were</p> <p>5 in terms of the four groups in the study?</p> <p>6 A. I'm trying to --</p> <p>7 Q. Take all the time you need.</p> <p>8 A. Yeah. Thank you. I think in this one</p> <p>9 particular table it's a little hard to tell. It does</p> <p>10 talk about the changes in oxygen in the fibrosis</p> <p>11 patients after inhalation. That paragraph below the</p> <p>12 table. N equals 1, only fibrosis patients. It</p> <p>13 describes the characteristics and oxygen saturations</p> <p>14 of the patients, and then it talked about reduction</p> <p>15 in the saturation after inhalation. So it's a little</p> <p>16 hard to tell.</p> <p>17 Q. Okay. And you were referring to the</p> <p>18 section between line 40 and line 54 in column 11; is</p> <p>19 that right?</p> <p>20 A. Yes.</p> <p>21 Q. Beginning, "this question was addressed in</p> <p>22 five patients"?</p> <p>23 A. Correct.</p> <p>24 Q. Okay. So looking at the 793 patent and</p> <p>25 going back to Table 2, do you know how many of the</p>
<p>118</p> <p>1 number of 45 patients with moderate to severe</p> <p>2 pre-capillary Pulmonary Hypertension were enrolled"?</p> <p>3 A. Yes.</p> <p>4 Q. And that's the same number we just pulled</p> <p>5 from Table 2?</p> <p>6 A. Yes.</p> <p>7 Q. Okay. Do you see at the bottom of this</p> <p>8 paragraph, I guess around line 44, there's a</p> <p>9 discussion of disease etiologies?</p> <p>10 A. Yes.</p> <p>11 Q. What's a disease etiology?</p> <p>12 A. Etiology means the cause of the disease.</p> <p>13 Q. Okay. And how many patients in this study,</p> <p>14 example 1, were PHILD patients?</p> <p>15 A. Four.</p> <p>16 Q. And which four were those?</p> <p>17 MR. SUKDUANG: Objection. Vague.</p> <p>18 Q. Strike that. What etiology did these --</p> <p>19 strike that. Are these the four pulmonary fibrosis</p> <p>20 patients?</p> <p>21 A. It says, "pulmonary fibrosis, N equals</p> <p>22 four".</p> <p>23 Q. So by simply elimination, 41 of the other</p> <p>24 patients were not PHILD patients; correct?</p> <p>25 A. Correct.</p>	<p>120</p> <p>1 pulmonary fibrosis patients received placebo?</p> <p>2 A. No.</p> <p>3 Q. Do you know how many pulmonary fibrosis</p> <p>4 patients received 30 micrograms of treprostinil?</p> <p>5 A. No.</p> <p>6 Q. Do you know how many pulmonary fibrosis</p> <p>7 patients received 45 micrograms of Treprostinil?</p> <p>8 A. No.</p> <p>9 Q. Do you know how many pulmonary fibrosis</p> <p>10 patients received 60 micrograms of treprostinil?</p> <p>11 A. No.</p> <p>12 Q. Okay. So based on the data in Table 2, in</p> <p>13 your opinion, is it possible to make any conclusions</p> <p>14 regarding the effects of hemodynamics or the</p> <p>15 hemodynamic effects of inhaled treprostinil on the</p> <p>16 four pulmonary fibrosis patients specifically?</p> <p>17 A. Not from this table, if we don't know which</p> <p>18 patients they were.</p> <p>19 Q. Let's turn to Table 3, which is on columns</p> <p>20 13 and 14, please.</p> <p>21 A. Okay.</p> <p>22 Q. And I believe you blow this table up in</p> <p>23 your declaration. So if you would like the bigger</p> <p>24 version in your declaration on page 26, I completely</p> <p>25 understand.</p>

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<p>121</p> <p>1 A. Okay.</p> <p>2 Q. Okay. And you can use whichever you like.</p> <p>3 Now, this is from a different study of inhaled</p> <p>4 treprostinil than Table 2; right?</p> <p>5 A. It's more than one study.</p> <p>6 Q. Okay. That's a great answer. Table 3 is a</p> <p>7 composite of 3 different studies; correct?</p> <p>8 A. Yes.</p> <p>9 Q. And Table 3 in particular shows the patient</p> <p>10 characteristics in baseline hemodynamic parameters</p> <p>11 for the patient population of these three studies; is</p> <p>12 that right?</p> <p>13 A. Yes.</p> <p>14 Q. And there's a disease etiology column. I</p> <p>15 believe it's the fourth; is that right?</p> <p>16 A. Yes.</p> <p>17 Q. And the etiology is either I, O, T, or F;</p> <p>18 right?</p> <p>19 A. Yes.</p> <p>20 Q. Okay. And F refers to pulmonary fibrosis?</p> <p>21 A. Yes.</p> <p>22 Q. Okay. Do the I, O, or T abbreviations</p> <p>23 refer to PHILD patients?</p> <p>24 A. No.</p> <p>25 Q. Okay. So if we wanted to know how many</p>	<p>123</p> <p>1 you?</p> <p>2 A. Well, ILO is Iloprost which is another</p> <p>3 inhaled prostacyclin. TRE is inhaled treprostinil.</p> <p>4 Q. Okay. So this was a head to head</p> <p>5 comparison of iloprost versus treprostinil?</p> <p>6 A. It was what they called randomized</p> <p>7 crossovers. They got both.</p> <p>8 Q. So if group 1A, if they got treprostinil,</p> <p>9 it was 7.5 micrograms of treprostinil?</p> <p>10 A. Yes.</p> <p>11 Q. Do you know how many breaths that</p> <p>12 treprostinil was dosed? Strike that. Do you know</p> <p>13 how many breaths the patients took while inhaling the</p> <p>14 treprostinil?</p> <p>15 A. Well, typically 7.5 micrograms would be</p> <p>16 about a breath.</p> <p>17 Q. So if you go into -- strike that. If you</p> <p>18 go to column 12, you'll see that around line 60</p> <p>19 there's a description of study 1, which goes --</p> <p>20 A. Where are we?</p> <p>21 Q. So column 12 in example 2, starting around</p> <p>22 line 60. There's a description of study 1?</p> <p>23 A. Yes, correct.</p> <p>24 Q. And then it continues to column 13 under</p> <p>25 the table?</p>
<p>122</p> <p>1 PHILD patients were in each study, and I guess</p> <p>2 subgroup within each of the three studies, we'd be</p> <p>3 looking at the F column; is that right?</p> <p>4 A. Yes.</p> <p>5 Q. So for example, in study group 1A there</p> <p>6 were four pulmonary fibrosis patients; right?</p> <p>7 A. Yes.</p> <p>8 Q. Okay. And if there was a zero, there were</p> <p>9 no pulmonary fibrosis patients; right? For example,</p> <p>10 2D?</p> <p>11 A. Correct.</p> <p>12 Q. Okay. And in these studies, the patients</p> <p>13 were dosed inhaled treprostinil by a nebulizer; is</p> <p>14 that right?</p> <p>15 A. Yes.</p> <p>16 Q. Okay. I want to go through this table and</p> <p>17 see if we can figure out what doses of treprostinil</p> <p>18 were applied to each of the -- the groups of</p> <p>19 pulmonary fibrosis patients. Is that an analysis you</p> <p>20 conducted as part of your analysis in this case?</p> <p>21 A. Yes. We can see it. It's right there.</p> <p>22 Q. Okay. So let's start with group 1. You</p> <p>23 can see under the table it says, group one</p> <p>24 correspondence to study 1. Group 1A, 7.5 grams ILO</p> <p>25 versus 7.5 micrograms TRE. What does that mean to</p>	<p>124</p> <p>1 A. Mm-hm, yes.</p> <p>2 Q. It says -- around line 43 in column 13 it</p> <p>3 says, "iloprost was inhaled at 4 micrograms per mil</p> <p>4 six-minute inhalation time. N equals 44.</p> <p>5 Treprostinil was inhaled at a concentration of 4</p> <p>6 micrograms per mil six-minute inhalation. N equals</p> <p>7 14. Did I get that right?</p> <p>8 A. Yes.</p> <p>9 Q. Okay. And if we look at 1A in Table 3,</p> <p>10 there are 14 patients in that group?</p> <p>11 A. Yes.</p> <p>12 Q. Okay. So over six minutes, would you</p> <p>13 expect a patient to take more than one breath?</p> <p>14 A. Again, I'd have to look specifically at the</p> <p>15 methodology, but this -- you know, usually it's</p> <p>16 individual breaths. It's not typically delivered as</p> <p>17 a continuous inhalation.</p> <p>18 Q. Okay.</p> <p>19 A. I guess that's a little unclear on how they</p> <p>20 actually delivered it.</p> <p>21 Q. Okay. So can you tell from the disclosure</p> <p>22 to the 793 patent how many micrograms for breath were</p> <p>23 dosed to the patients in group 1A?</p> <p>24 A. I mean, it's written here based on the</p> <p>25 device they use in the treprostinil solution that</p>

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<p style="text-align: right;">125</p> <p>1 would correspond to 15 micrograms of treprostinil, as 2 written at the bottom of that paragraph. 3 Q. So I guess my question is, in group 1A, how 4 many micrograms per breath were administered, if you 5 can tell? 6 A. It doesn't give it per breath. That's the 7 problem. It says 15 micrograms treprostinil. I'm 8 just saying what we read here. 9 Q. Okay. And if we go down to group 1B in 10 Table 3 it says, "7.5 grams iloprost versus 11 15 micrograms of treprostinil, six-minute inhalation 12 time." 13 A. Yeah. 14 Q. Can you tell how many micrograms per breath 15 were administered there? 16 A. Twice as much as the last one. 17 Q. Right, but can you tell the actual -- 18 A. Again, it's not written the way -- it's not 19 individual breaths the way it's written here. 20 Q. Right. 21 A. So it's -- that's all I can say. 22 Q. Okay. 23 A. Hard to tell. 24 Q. And how about group 1C? Same thing? 25 A. Yeah. Looks like they gave the same dosage</p>	<p style="text-align: right;">127</p> <p>1 A. As you can see. You can see it right 2 there. 30 micrograms, 60 micrograms, 90 micrograms, 3 120 micrograms over six minutes. 4 Q. Okay. But you can't tell from this 5 description what the micrograms per breath were? 6 A. It's not expressed that way; correct. 7 Q. Okay. And then let's talk about study 3. 8 And I believe this is described column 13 line 65 and 9 it continues onto column 14. There are -- would you 10 agree that there were also five groups in study 3. 11 A. Correct. 12 Q. Okay. And if we look under Table 3, the 13 particular groups are separated from particular 14 pulses of treprostinil at particular concentrations; 15 is that right? 16 A. Yes. 17 Q. Okay. But in all cases, the patients are 18 getting 15 micrograms of inhaled treprostinil, just 19 in a different number of pulses and in different 20 numbers of concentrations; is that right? 21 A. 15 micrograms. 22 Q. Okay. I believe it says at line 66, "the 23 primary objective was to explore the shortest 24 possible inhalation time for a 15 microgram dose of 25 inhaled treprostinil"; is that right?</p>
<p style="text-align: right;">126</p> <p>1 of treprostinil but they gave it over shorter 2 inhalation time. 3 Q. Okay. Let's talk about study 2. That's 4 the -- I believe it's 2A through 2E in Table 3. It's 5 described in column 13 from lines 51 through 64. Do 6 you see here that the inhalation time for study 2 was 7 six minutes in all groups? 8 A. Yes. 9 Q. Okay. And then there were five groups in 10 this study; right? 11 A. Yes. 12 Q. There was placebo was one group; right? 13 A. Yes. 14 Q. And then there was 30, 60, 90, or 15 120 micrograms of treprostinil; is that right? 16 A. Yes. 17 Q. Can you tell for any of those five groups 18 how many micrograms per breath were administered? 19 A. I mean, you have the dosage of treprostinil 20 they got. Again, it's a little bit unclear how they 21 delivered it other than through the nebulizer, 22 whether it was continuous versus individual breaths. 23 Although, it looks, at least for study 2 -- so it 24 just gives the dose that they got. 25 Q. Okay. So it doesn't --</p>	<p style="text-align: right;">128</p> <p>1 A. Yes. 2 Q. Okay. And then it says, "the drug was 3 applied -- this is from column 14, line 2. The drug 4 was applied in 18, 9, 3, 2, or 1 breaths." Did I get 5 that right? 6 A. Where are we now? 7 Q. Okay. So if you go on column 14, lines 2 8 and 3. 9 A. 14. Lines 2 or 3? 10 Q. I'm sorry. My fault. That's totally my 11 fault. It would be 34 and 35. I apologize. 12 A. Okay. Yeah. I got it. 13 Q. Okay. So now we know the amount of breaths 14 that were applied in this study; right? 15 A. Yes. 16 Q. Okay. And everybody's getting a 15 17 microgram dose, it's just a question of how many 18 breaths; right? 19 A. Yes. 20 Q. Okay. And if you go to the chart 21 underneath Table 3, do you see that the five groups 22 are spelled out there? 23 A. Yes. 24 Q. And I think they say pulses. Do you 25 understand pulses to be equivalent to breaths here?</p>

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<p>129</p> <p>1 A. Yes.</p> <p>2 Q. Okay. So -- and if we go back up to</p> <p>3 Table 3, there were only 2 pulmonary fibrosis</p> <p>4 patients included in this study 3; correct?</p> <p>5 A. Yes.</p> <p>6 Q. One was in group 3B; right?</p> <p>7 A. Yes.</p> <p>8 Q. And one was in group 3C; correct?</p> <p>9 A. Yes.</p> <p>10 Q. Okay. And so the patient in group 3B</p> <p>11 received 15 micrograms of treprostinil in 9 breaths;</p> <p>12 is that correct?</p> <p>13 A. Yes.</p> <p>14 Q. Okay. And the patient in group 3C received</p> <p>15 15 micrograms of treprostinil in 3 breaths; is that</p> <p>16 correct?</p> <p>17 A. Yes.</p> <p>18 Q. Okay. I want to go back to Table 2 for a</p> <p>19 minute. This is on column 11. I'll look back to</p> <p>20 Exhibit 1, your declaration. In paragraph 66 you</p> <p>21 reproduce Table 2. Do you see that?</p> <p>22 A. Yes.</p> <p>23 Q. The last sentence on page 25 says, "in my</p> <p>24 opinion, the magnitude of the improvements reported</p> <p>25 for PVR and MPAP would be expected to translate into</p>	<p>131</p> <p>1 and 16?</p> <p>2 A. Yes.</p> <p>3 Q. What do you understand them to be?</p> <p>4 A. Like you said, they're articles. An</p> <p>5 article on reporting the INCREASE trial.</p> <p>6 Q. And you reviewed this article -- strike</p> <p>7 that. When was the first time you saw this article?</p> <p>8 Exhibit 15?</p> <p>9 A. Upon publication.</p> <p>10 Q. And what was your reaction upon seeing this</p> <p>11 article?</p> <p>12 MR. SUKDUANG: Objection. Vague.</p> <p>13 THE WITNESS: I don't recall having a</p> <p>14 specific reaction.</p> <p>15 Q. Okay. And this is the New England Journal</p> <p>16 of Medicine publication describing the results of the</p> <p>17 INCREASE study; is that correct?</p> <p>18 A. Yes.</p> <p>19 Q. And Exhibit 16, are you familiar with that</p> <p>20 as well?</p> <p>21 A. Yes.</p> <p>22 Q. What do you understand Exhibit 16 to be?</p> <p>23 A. This is just a supplementary appendix to</p> <p>24 that article.</p> <p>25 Q. In general, what's a supplementary</p>
<p>130</p> <p>1 an improvement in exercise capacity." Did I get that</p> <p>2 right?</p> <p>3 A. Yes.</p> <p>4 Q. Okay. When you say, "magnitude of</p> <p>5 improvements", are you talking about all three active</p> <p>6 arms of that study or are you referring to a</p> <p>7 particular dosage?</p> <p>8 A. All three.</p> <p>9 Q. So in your opinion, the magnitude of</p> <p>10 improvements in even the 30 microgram arm would be</p> <p>11 expected to translate to an improvement in exercise</p> <p>12 capacity?</p> <p>13 A. Yes.</p> <p>14 Q. Okay. I'm going to mark three in a row</p> <p>15 here. We can start with these and then I'll mark the</p> <p>16 third one later.</p> <p>17 (Exhibit 15 marked for identification.)</p> <p>18 (Exhibit 16 marked for identification.)</p> <p>19 Q. Dr. Channick, the court reporter's handed</p> <p>20 you two exhibits marked 15 and 16. Exhibit 15 is an</p> <p>21 article from the New England Journal of Medicine from</p> <p>22 Waxman et al, entitled, "pulmonary hypertension due</p> <p>23 to interstitial lung disease", and Exhibit 16 is the</p> <p>24 supplementary appendix for that article.</p> <p>25 Doctor, are you familiar with Exhibits 15</p>	<p>132</p> <p>1 appendix?</p> <p>2 A. A supplementary appendix is basically</p> <p>3 everything else that couldn't get into the main</p> <p>4 article due to size limitations and what not, but</p> <p>5 data that was collected and is reported in that</p> <p>6 appendix.</p> <p>7 Q. Okay. Excellent. Now, you have cited this</p> <p>8 article, the INCREASE study, in your declaration</p> <p>9 regarding anticipation; correct?</p> <p>10 A. Yes.</p> <p>11 Q. Do you -- in offering your opinions in this</p> <p>12 case, did you review the file history of the 327</p> <p>13 patent?</p> <p>14 A. I don't recall the file history</p> <p>15 specifically.</p> <p>16 Q. Okay. Do you understand what a file</p> <p>17 history is?</p> <p>18 A. It seems like it's self-explanatory, maybe.</p> <p>19 Q. Sure. Do you understand a file history or</p> <p>20 prosecution history is generally the record of the</p> <p>21 communications between the patent applicant and</p> <p>22 patent examiner?</p> <p>23 A. That makes sense.</p> <p>24 Q. Have you reviewed file histories of patents</p> <p>25 before?</p>

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<p>133</p> <p>1 A. No.</p> <p>2 Q. And you didn't review it in this case?</p> <p>3 A. Not that I remember, no.</p> <p>4 Q. Do you know if the examiner who evaluated</p> <p>5 and issued the 327 patent was aware of Exhibit 15?</p> <p>6 MR. SUKDUANG: Lack of foundation.</p> <p>7 THE WITNESS: I have no knowledge of that.</p> <p>8 Q. If it turned out that the examiner who</p> <p>9 issued the 327 patent was aware of and had reviewed</p> <p>10 this Waxman paper, would that affect your opinions in</p> <p>11 any way in this matter?</p> <p>12 MR. SUKDUANG: Lack of foundation.</p> <p>13 THE WITNESS: No.</p> <p>14 Q. We're going to look at all three together.</p> <p>15 Dr. Channick, the court reporter's handed you what's</p> <p>16 been marked as Exhibit 17.</p> <p>17 (Exhibit 17 marked for identification.)</p> <p>18 Q. This is a document bearing Bates Numbers</p> <p>19 LIQ_PH-ILD_00000185 through 215. Dr. Channick, do</p> <p>20 you recognize Exhibit 17?</p> <p>21 A. Yes.</p> <p>22 Q. What is Exhibit 17?</p> <p>23 A. It's the published study as registered on</p> <p>24 clinicaltrials.gov for the INCREASE trial.</p> <p>25 Q. Okay. And at page 29 of your declaration,</p>	<p>135</p> <p>1 course of a study.</p> <p>2 Q. Okay. Let's turn to page ending 194, or 10</p> <p>3 of 31, in Exhibit 17. Do you see that there is a box</p> <p>4 entitled, "arms and interventions"?</p> <p>5 A. Yes.</p> <p>6 Q. Okay. And do you see the third row in that</p> <p>7 table is, active comparator, active inhaled</p> <p>8 treprostnil?</p> <p>9 A. Yes.</p> <p>10 Q. It says, "active treprostnil for</p> <p>11 inhalation solution six-minutes s per mill delivered</p> <p>12 by an ultrasonic nebulizer, which admits a dose of</p> <p>13 approximately 6 micrograms per breath, inhaled 4</p> <p>14 times daily and titrated up to a maximum of 12</p> <p>15 breaths four times daily. Did I get that right?</p> <p>16 A. Yes.</p> <p>17 Q. Okay. So according to this protocol, what</p> <p>18 was the starting dose for a patient in terms of how</p> <p>19 many breaths they would be administered?</p> <p>20 A. Four breaths. You're talking about -- I</p> <p>21 mean, 6 micrograms is typically 1 breath. 12 breaths</p> <p>22 would be, you know, 12 times 6.</p> <p>23 Q. It says, titrated up to a maximum of 12</p> <p>24 breaths four times daily?</p> <p>25 A. Correct.</p>
<p>134</p> <p>1 Exhibit 1, you refer to a document called the 2017</p> <p>2 INCREASE study description. This is page 29: I just</p> <p>3 want to confirm it's the same document?</p> <p>4 A. Yes.</p> <p>5 Q. Okay. Dr. Channick, is this a document</p> <p>6 that you retrieved from clinicaltrials.gov for</p> <p>7 purposes of this declaration, or was it provided to</p> <p>8 you by counsel?</p> <p>9 A. Provided by counsel.</p> <p>10 Q. Dr. Channick, have you confirmed that the</p> <p>11 protocol described in Exhibit 17 is actually the</p> <p>12 protocol that was used to conduct the INCREASE study</p> <p>13 as resulted in the Waxman article, Exhibit 15?</p> <p>14 A. I guess you have to explain what you mean</p> <p>15 by confirmed that it was the protocol used. I mean,</p> <p>16 it's generally how it works. You have to register a</p> <p>17 study and describe the methodology. There may be</p> <p>18 amendments to studies that occurred at some point.</p> <p>19 Q. Let me ask a better question. Do you know</p> <p>20 if this protocol was amended prior to the INCREASE</p> <p>21 study being conducted?</p> <p>22 A. Not necessarily prior to it being</p> <p>23 conducted, but certainly during the conduct of the</p> <p>24 study. I wasn't involved in the Increase study, but</p> <p>25 there are amendments that often occur during the</p>	<p>136</p> <p>1 Q. So where was the start of the -- let me</p> <p>2 backup. What's a titration?</p> <p>3 A. Titration is when you're changing -- going</p> <p>4 up or down on a dose.</p> <p>5 Q. So if you're titrating; correct?</p> <p>6 A. Correct.</p> <p>7 Q. So according to this protocol, what is the</p> <p>8 starting dose that's applied?</p> <p>9 MR. SUKDUANG: If you need to look at the</p> <p>10 rest of the document, you can.</p> <p>11 THE WITNESS: It's going to be at least</p> <p>12 6 micrograms. So that would be the starting dose --</p> <p>13 wouldn't be less than that, since that's the lowest</p> <p>14 you can go.</p> <p>15 Q. Right.</p> <p>16 A. We're referring now to this document?</p> <p>17 Q. Exhibit 17, the protocol.</p> <p>18 A. It says it's going to be at least</p> <p>19 6 micrograms in the protocol. So that would be at</p> <p>20 least 1 breath in the protocol. It doesn't specify</p> <p>21 that every patient started with the same number of</p> <p>22 breaths. It gives the minimum and then the maximum.</p> <p>23 Q. Okay. And then they would be titrated up</p> <p>24 depending on their ability to tolerate the</p> <p>25 medication; is that right?</p>

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<p>137</p> <p>1 A. Yes, that's how we've always used this 2 drug. 3 Q. Okay. Now, let's compare that to page 3 of 4 7 of Exhibit 15, which is the INCREASE study 5 publication? 6 MR. SUKDUANG: I'm sorry. Which page 7 number? 8 MR. ROMEO: 327. 9 MR. SUKDUANG: Thank you. 10 Q. Do you see on the left-hand column on 11 page 327, there's a section called, "trial 12 procedures"? 13 A. Yes. 14 Q. And about -- strike that. In the second 15 paragraph under trial procedures, the third sentence 16 reads, "the first dose of trial drug three breaths 17 was administered in the clinic, followed by an at 18 least one hour observation period." Did I get that 19 right? 20 A. Yes. 21 Q. Okay. So in the New England Journal 22 publication, the starting dose is listed as 3 23 breaths; correct? 24 A. Yes. 25 Q. Okay. Let's go back to Exhibit 17. Now</p>	<p>139</p> <p>1 Q. If we go to Exhibit 15, the INCREASE trial, 2 do you see on page 326 there's a heading, "trial 3 population"? 4 A. Yes. 5 Q. Do you see that under trial population, 6 they had a definition for group 3 Pulmonary 7 Hypertension? 8 A. Yes. 9 Q. Is the inclusion criteria for group 3 10 Pulmonary Hypertension listed in the New England 11 Journal of Medicine the same as the inclusion 12 criteria listed in the 2017 protocol, Exhibit 17? 13 A. Yeah. They made a very small change in the 14 thresholds, the numbers for what would qualify for 15 the study. So they went from four to three wood 16 units, presumably to increase enrollment. We can 17 look and see what they actually turned out to have, 18 whether the population was what was similar to what 19 the first criteria were, but they made a very small 20 tweak in the resistance cut off to get into the 21 study, and a little tweak in the pressure cut off to 22 get into the study. 23 So very small change in the hemodynamic 24 inclusion criteria. Not a, in my opinion, a 25 significant change of anything to me.</p>
<p>138</p> <p>1 page ending 196. 12 of 31. Do you see here that the 2 inclusion criteria for the study are listed here? 3 A. Yes. 4 Q. Do you know if those inclusion criteria 5 were amended for the final study? 6 A. I don't know that, no. We can certainly 7 look at that. 8 Q. Sure. Let's start at entry number 4 on 9 page 196. It says here, "subjects are required to 10 have an Right Heart Catheterization, RHC, within one 11 year prior to randomization with the following 12 documented parameters. 13 Pulmonary vascular resistance, PVR greater 14 than or equal to four wood units, WU, and number 2, a 15 left ventricular and diastolic pressure. LVEDP or 16 pulmonary capillary wedge pressure, PCWP of less than 17 or equal to 12 milligrams of mercury, millimeters of 18 mercury. If PVR greater than or equal to four wood 19 units to less than 6.25 wood units or less than or 20 equal to 15 millimeters of mercury, if PVR is greater 21 than or equal to 6.25 wood units, and number 3, a 22 mean pulmonary arterial pressure MPAP of greater than 23 or equal to 30 millimeters of mercury." 24 Did I get that mostly right? 25 A. Yes.</p>	<p>140</p> <p>1 Q. And if you pull out Exhibit 16, which I 2 believe is the supplementary materials, I think that 3 lists additional detail on inclusion and exclusion 4 criteria. Can you identify any other differences 5 between what was reported in the New England Journal 6 of Medicine and what is present in Exhibit 17? 7 MR. SUKDUANG: Wait a second. You asked 8 him to pull out Exhibit 16. 9 MR. ROMEO: Yup. 10 MR. SUKDUANG: What do you want him to do 11 with 16 and 17? Or 15 and 17. 12 MR. ROMEO: Apologies. If it wasn't clear, 13 we discussed that 16 is the supplementary appendix to 14 16, both of which were in the New England Journal, 15 and 16 contains more details on the inclusion and 16 exclusion criteria for the study, and I'm asking him 17 to confirm if there are any other differences between 18 the protocol he's relying on, Exhibit 17, and what's 19 been reported in the New England Journal. 20 MR. SUKDUANG: Hold on. I'm going to 21 object as beyond the scope. They're very large 22 documents. I'm just hoping you prepared if this 23 takes a while, because you haven't provided any 24 direction. Go ahead, Dr. Channick. 25 THE WITNESS: So just specifically looking</p>

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<p>141</p> <p>1 at those two things, the inclusion and exclusion 2 criteria, there were a few other very small 3 differences. We can just walk through them. In the 4 description of the study in clinical trials, they had 5 an upper age limit of 79, which it looks like they 6 removed in the final protocol. So rather than 18 to 7 79, it was 18 or older. 8 So it looks like they removed the upper age 9 cut off, so broadened it a bit. We talked about the 10 catheterization differences. It looks like to me 11 that diffusing capacity was removed as an inclusion 12 criteria. So that's just one of the measurements. I 13 think that's kind of it for the inclusion criteria. 14 So there's minor differences to really, I think -- I 15 may be speculating, but to broaden the population a 16 bit. 17 But then the exclusion criteria. Offhand, 18 I can't find any big -- any differences in that. 19 Q. Okay. 20 A. But if you see any, feel free to point them 21 out. 22 Q. Thank you. I think you can put those 23 aside. Dr. Channick, the court reporter's handed you 24 what's marked Exhibit 18. 25 (Exhibit 18 marked for identification.)</p>	<p>143</p> <p>1 based on an earnings call transcript? 2 A. No. 3 Q. Would you ever make a prescribing decision 4 based on an earnings call transcript? 5 A. No. 6 Q. All right. Let's turn to page 4 of this 7 document under the heading, presentation. Do you see 8 that one of the participants in this call is doctor 9 Martine Rothblatt? 10 A. Yes. 11 Q. Chairman and CEO of United Therapeutics? 12 A. Yes. 13 Q. Do you know what document Dr. Rothblatt's 14 degree is in? 15 A. No. 16 Q. Do you know if she meets the requirements 17 for a person of ordinary skill in the art? 18 A. She's not a medical doctor. 19 Q. So does she meet your definition of a 20 person of ordinary skill in the art? 21 A. No. 22 Q. Okay. If you go down to -- let's see. You 23 see that there's a paragraph in the middle of the 24 page beginning, today's remarks? 25 A. Yes.</p>
<p>142</p> <p>1 Q. This is a document bearing Bates numbers 2 LIQ_PH-ILV_0000001 through 12. Dr. Channick, do you 3 recognize Exhibit 18? 4 A. Yes. 5 Q. What is Exhibit 18? 6 A. It's a United Therapeutics Corporation 7 earnings call transcript from May 2, 2018. 8 Q. And this is a document that you cite in 9 your declaration; is that correct? 10 A. Yes. 11 Q. Was this a document that you located or a 12 document that was provided by counsel? 13 A. Provided by counsel. 14 Q. In the course of your work as a 15 pulmonologist, is it part of your ordinary practice 16 to review corporate earnings calls for publicly 17 traded companies? 18 A. No. 19 Q. In your opinion, Doctor, would a person of 20 ordinarily skill in the art to which the 327 patent 21 retains, would use earnings calls for companies like 22 United Therapeutics. 23 A. I don't know the answer to that. Some 24 would. Some wouldn't. 25 Q. Have you ever made a prescribing decision</p>	<p>144</p> <p>1 Q. It reads, "today's remarks may discuss the 2 progress and results of clinical trials or other 3 developments with respect to our products. These 4 remarks are intended to solely educate investors and 5 are not intended to serve as the basis for medical 6 decision making or to suggest that the products are 7 safe and effective for any unapproved or 8 investigational uses. Full prescribing information 9 for the products is available on our website." Did I 10 get that right? 11 A. Yes, standard disclaimer. 12 Q. And that's consistent with your testimony 13 that you had not used the contents of an earning call 14 to make a prescribing decision; is that correct? 15 A. Correct. 16 Q. Okay. You can put that aside. Dr. 17 Channick, the court reporter's handed you what's been 18 marked as Exhibit 19. 19 (Exhibit 19 marked for identification.) 20 Q. This is a document Bearing Bates number 21 PHILD_increase. Do you recognize Exhibit 19? 22 A. Yes. 23 Q. Is this the Agarwal 2015 reference you 24 refer to in your declaration? 25 A. Yes.</p>

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<p>145</p> <p>1 Q. And this is an -- what type of publication</p> <p>2 is this, to your knowledge?</p> <p>3 A. An abstract.</p> <p>4 Q. When you say an abstract, what do you mean?</p> <p>5 A. It's the summary of a study that was done</p> <p>6 that's presented at a meeting typically and published</p> <p>7 as an abstract.</p> <p>8 Q. And the authors of this abstract are M</p> <p>9 Agarwal and AB Waxman?</p> <p>10 A. Yes.</p> <p>11 Q. And AB Waxman, that's the first author of</p> <p>12 the Increase study publication, Exhibit 15 we just</p> <p>13 looked at?</p> <p>14 A. Yes. Yes.</p> <p>15 Q. Okay. If we go to methods, are you there?</p> <p>16 A. Yes.</p> <p>17 Q. It says, "we followed 35 WHO group 3 PHPTS</p> <p>18 treated with IRE for 6-months. 15 had obstructive,</p> <p>19 15 restricted disease, and five were classified as</p> <p>20 assigned to there classified as mixed." Did I get</p> <p>21 that right?</p> <p>22 A. Close enough.</p> <p>23 Q. Okay. So suffice it to say there are 35</p> <p>24 patients in this study that were treated with inhaled</p> <p>25 treprostinil for six months?</p>	<p>147</p> <p>1 Q. And what do you understand a retrospective</p> <p>2 trial to be?</p> <p>3 A. A retrospective trial is looking back at</p> <p>4 what you did rather than what you're going to do.</p> <p>5 Some might call it real world data, which is very</p> <p>6 important because it's what actually is done in</p> <p>7 practice. So in their practice, they treated these</p> <p>8 patients with inhaled treprostinil, 20 of who would</p> <p>9 qualify as ILDPH.</p> <p>10 And then they went back and looked at how</p> <p>11 these patients have done. That's the retrospective</p> <p>12 part of it. That's why we call it a real world trial</p> <p>13 as opposed to a prospective trial.</p> <p>14 Q. There was no placebo included in this</p> <p>15 trial; correct?</p> <p>16 A. Correct.</p> <p>17 Q. Why is a placebo included in off?</p> <p>18 A. Why is a placebo included --</p> <p>19 Q. Yeah. Why use a placebo on --</p> <p>20 A. Again, it's more of an involved answer.</p> <p>21 When you're doing a prospective study, and I talked</p> <p>22 about it before, you need to randomize patients to</p> <p>23 meet the standard for drug approvals where you need</p> <p>24 to go to a phase -- what we call RCT, or randomized</p> <p>25 control trial.</p>
<p>146</p> <p>1 A. Yes.</p> <p>2 Q. 15 were classified as having obstructive</p> <p>3 disease; correct?</p> <p>4 A. Yes.</p> <p>5 Q. What's obstructive disease in this context?</p> <p>6 A. That would likely be COPD patients.</p> <p>7 Q. Okay. And then another 15 were reported as</p> <p>8 having restrictive disease; is that right?</p> <p>9 A. Yes.</p> <p>10 Q. And so what is restrictive disease in this</p> <p>11 context?</p> <p>12 A. That would be PHILD patients.</p> <p>13 Q. And then five had a mixed phenotype; is</p> <p>14 that right?</p> <p>15 A. Yeah. That might be what we call CPFE,</p> <p>16 which is also -- it's fibrosis with obstruction on</p> <p>17 top of it.</p> <p>18 Q. Okay.</p> <p>19 A. Also included in the INCREASE trial.</p> <p>20 Q. Okay. Now, was this a randomized clinical</p> <p>21 trial?</p> <p>22 A. No.</p> <p>23 Q. Was this what you might call a</p> <p>24 retrospective trial?</p> <p>25 A. Yes.</p>	<p>148</p> <p>1 There can be what we call placebo effects</p> <p>2 where patients can get better, even on the placebo.</p> <p>3 So that gives you some comparison in certain</p> <p>4 segments.</p> <p>5 Q. So in other words a placebo is a form of a</p> <p>6 negative control?</p> <p>7 A. Yeah, you could say that.</p> <p>8 Q. Now if we look at the results part of</p> <p>9 Agarwal, would you agree that both the restrictive</p> <p>10 patients and the obstructive patients -- so in other</p> <p>11 words, both the COPD and ILD patients, both showed an</p> <p>12 increase in their six-minute walk distance?</p> <p>13 A. Yes.</p> <p>14 Q. Okay. Doctor, I believe you've given the</p> <p>15 opinion, and you can correct me if I'm wrong, that</p> <p>16 this Agarwal abstract would have given a person of</p> <p>17 ordinary skill a reasonable expectation that inhaled</p> <p>18 treprostinil could be successfully used to improve</p> <p>19 exercise capacity in PHILD; is that correct?</p> <p>20 A. Yes, that's one of the bits of evidence</p> <p>21 that would allow that conclusion.</p> <p>22 Q. Would a similar expectation also exist as</p> <p>23 to COPD patients in your opinion?</p> <p>24 A. If there were other factors. It's not</p> <p>25 based on this one abstract. I would look at whether</p>

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<p>149</p> <p>1 there are other published studies, other teachings</p> <p>2 that would allow me to make that conclusion. So if</p> <p>3 this was all I had, one thing, I probably wouldn't</p> <p>4 say that for COPD.</p> <p>5 Q. Now, you're aware that United Therapeutics</p> <p>6 conducted a phase 3 trial of inhaled treprostinil and</p> <p>7 COPD; correct?</p> <p>8 A. I had heard something about that. I was</p> <p>9 not involved with it, though.</p> <p>10 Q. Do you understand that trial to be called</p> <p>11 the perfect study?</p> <p>12 A. I don't know the name of it.</p> <p>13 Q. Okay. Do you know what the result of that</p> <p>14 trial was?</p> <p>15 A. No.</p> <p>16 Q. Do you know if that trial was discontinued</p> <p>17 for futility?</p> <p>18 A. I honestly didn't follow that trial so I</p> <p>19 don't know.</p> <p>20 Q. You can put that aside. Doctor, the court</p> <p>21 reporter's handed you what's been marked as</p> <p>22 Exhibit 20.</p> <p>23 (Exhibit 20 marked for identification.)</p> <p>24 Q. This is a document bates numbers</p> <p>25 LIQ_PH-IOD_00000226 through 246. Doctor, do you</p>	<p>151</p> <p>1 treprostinil.</p> <p>2 Q. And what dosage form of treprostinil were</p> <p>3 the patients in this study administered?</p> <p>4 A. It was a parenteral treprostinil.</p> <p>5 Q. And in this context, what does parenteral</p> <p>6 mean?</p> <p>7 A. It typically would mean either -- for</p> <p>8 treprostinil it would be either intravenous or</p> <p>9 subcutaneous as a continuous infusion.</p> <p>10 Q. So not inhaled?</p> <p>11 A. Correct.</p> <p>12 Q. And how many patients were in this study?</p> <p>13 A. 15.</p> <p>14 Q. Okay. Let's turn to Table 2, please.</p> <p>15 Internal page 125, Bates 228. Would you agree that</p> <p>16 Table 2 summarizes the results of pulmonary function</p> <p>17 testing and other assays that were performed on this</p> <p>18 patient population?</p> <p>19 A. Yes.</p> <p>20 Q. And in particular, the data reported is the</p> <p>21 baseline characteristic as well as what happened</p> <p>22 after 12 weeks of treatment; is that right?</p> <p>23 A. Yes.</p> <p>24 Q. What's baseline?</p> <p>25 A. What do you mean?</p>
<p>150</p> <p>1 recognize Exhibit 20?</p> <p>2 A. Yes.</p> <p>3 Q. What is Exhibit 20?</p> <p>4 A. This is an article on changes in right</p> <p>5 heart human dynamics, echocardiographic function in</p> <p>6 advanced Pulmonary Hypertension and right hand</p> <p>7 function fibrosis, so it's a study of that patient</p> <p>8 population published in 2014.</p> <p>9 Q. Okay. And this is a paper that you cite in</p> <p>10 your declaration, Exhibit 1; correct?</p> <p>11 A. Yes.</p> <p>12 Q. Okay. Was this a prospective or</p> <p>13 retrospective study that's described in Exhibit 20,</p> <p>14 Sagar 2014?</p> <p>15 A. This was also a real world study. Whether</p> <p>16 it was retrospective, in other words had already done</p> <p>17 the treatment and looked back, or whether they looked</p> <p>18 at the real world prospectively is not entirely</p> <p>19 specified. It was a single arm study, though. It's</p> <p>20 not to be vague, but it doesn't specifically say</p> <p>21 these are patients who got this therapy and then we</p> <p>22 looked back.</p> <p>23 It was open label, though, looking at</p> <p>24 patients with PH who were recruited to the study who</p> <p>25 had pulmonary fibrosis and got treated with</p>	<p>152</p> <p>1 Q. So what does baseline refer to here?</p> <p>2 A. Before treatment.</p> <p>3 Q. Okay. And then there's a column that says,</p> <p>4 "P value". Do you see that?</p> <p>5 A. Yes.</p> <p>6 Q. What is P value in this context?</p> <p>7 A. P value is a measure of what we call</p> <p>8 statistical significance based on, sort of, standard</p> <p>9 statistical methods that are done.</p> <p>10 Q. Is P value like baseball scoring or golf</p> <p>11 scoring? By that I mean, is a lower number better or</p> <p>12 is a higher number better?</p> <p>13 A. Lower number is better.</p> <p>14 Q. Okay. And what level of P value do you</p> <p>15 need to see in your experience before you would</p> <p>16 consider a measure statistically significant?</p> <p>17 A. Complicated question. But one of the</p> <p>18 accepted thresholds is .05, which just to put it in</p> <p>19 terms people can understand, means that there's a 95</p> <p>20 or greater percent chance that a difference you see</p> <p>21 is not by chance alone. So think of that just for a</p> <p>22 second. Bear with me.</p> <p>23 It means that .06 which you might say is</p> <p>24 not statistically significant, a 94 percent chance</p> <p>25 that a difference is not by chance alone. So lower</p>

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<p>153</p> <p>1 is better is what I'll say.</p> <p>2 Q. Okay. Could you turn to paragraph 80 of</p> <p>3 your declaration, please? It's on page 32?</p> <p>4 A. Yes.</p> <p>5 Q. And would you agree between paragraphs 79</p> <p>6 and 81, you're summarizing this reference, Saggar</p> <p>7 2014, Exhibit 20?</p> <p>8 A. Yes.</p> <p>9 Q. Okay. In paragraph 80, the last sentence</p> <p>10 says, "further, the authors reported a change in FVC</p> <p>11 present predicted from 62 percent at baseline to</p> <p>12 63 percent after 12 weeks." Did I get that right?</p> <p>13 A. Yes.</p> <p>14 Q. Was that result statistically significant</p> <p>15 according to Saggar?</p> <p>16 A. No.</p> <p>17 Q. So what is the significance -- what would</p> <p>18 the significance of that result be to a person of</p> <p>19 ordinary skill in the art in your opinion?</p> <p>20 A. It would be what it was. It would be a one</p> <p>21 percent increase in FVC, which was almost identical,</p> <p>22 by the way, to the increase in FVC in the Increase</p> <p>23 study. What the P value is in a very small study</p> <p>24 that wasn't designed in that way is irrelevant. So I</p> <p>25 would look at that for what it was. A 1 percent</p>	<p>155</p> <p>1 Q. Okay. Dr. Channick, in your opinion, when</p> <p>2 would a POSA have understood that inhaled</p> <p>3 treprostinil necessarily and inevitably improves</p> <p>4 exercise capacity in a PHILD patient?</p> <p>5 A. When was the first time they would have</p> <p>6 known that?</p> <p>7 Q. Correct.</p> <p>8 A. Would have understood that?</p> <p>9 Q. Yup.</p> <p>10 A. I mean, I think we've kind of talked about</p> <p>11 the previous patent, 793 patent. We've talked about</p> <p>12 the 2014 Agarwal. We've talked about Saggar.</p> <p>13 Certainly back that far. And well before INCREASE,</p> <p>14 certainly. I should add in, you know, numerous years</p> <p>15 of clinical experience with the drug in patients who</p> <p>16 had PHILD since it was approved, essentially.</p> <p>17 Q. Dr. Channick, as part of your analysis</p> <p>18 regarding the validity of the claims of the 327</p> <p>19 patent, did you assume that a person of ordinary</p> <p>20 skill would have been in possession of the Waxman</p> <p>21 article?</p> <p>22 MR. SUKDUANG: Objection. Vague.</p> <p>23 THE WITNESS: Not necessarily, no.</p> <p>24 Q. Okay. So you didn't assume that a person</p> <p>25 of ordinary skill would have been aware of the Waxman</p>
<p>154</p> <p>1 increase in FVC, increase 1.1 percent increase in FVC</p> <p>2 and the P value becomes -- when you're talking about</p> <p>3 1 percent, meaningless to clinicians.</p> <p>4 Q. We've been going now for a little over an</p> <p>5 hour. Is now a good time for a break?</p> <p>6 A. Sure.</p> <p>7 VIDEOGRAPHER: We're going off the record.</p> <p>8 The time is 2:00 P.M.</p> <p>9 (Recess taken.)</p> <p>10 VIDEOGRAPHER: We're back on the record.</p> <p>11 The time is 2:25 P.M.</p> <p>12 Q. Welcome back, Dr. Channick. I'd like to go</p> <p>13 to your declaration, Exhibit 1, page 36. In</p> <p>14 particular paragraph 88, please.</p> <p>15 A. Okay.</p> <p>16 Q. It says, "second, a POSA would have</p> <p>17 understood that inhaled treprostinil necessarily and</p> <p>18 inevitably improves exercise capacity in a patient</p> <p>19 having PHILD. The INCREASE study showed, quote,</p> <p>20 significant improvement in exercise capacity as</p> <p>21 evidenced by changes in the six-minute walk distance,</p> <p>22 end quote."</p> <p>23 And then you provide Figure 2 from the</p> <p>24 Waxman article; is that correct.</p> <p>25 A. Yes.</p>	<p>156</p> <p>1 article?</p> <p>2 A. They may or may not have been.</p> <p>3 Q. Dr. Channick, the court reporter's handed</p> <p>4 you what's been marked as Exhibit 21.</p> <p>5 (Exhibit 21 marked for identification.)</p> <p>6 Q. This is a review article entitled,</p> <p>7 "clinical perspective with long-term pulsed inhaled</p> <p>8 nitric oxide for the treatment of pulmonary arterial</p> <p>9 hypertension." Published in Pulmonary Circulation</p> <p>10 April/June 2012?</p> <p>11 Dr. Channick, do you recognize Exhibit 21?</p> <p>12 A. Yes.</p> <p>13 Q. What is Exhibit 21?</p> <p>14 A. It's an article that I wrote with a few</p> <p>15 other authors on pulse delivery of nitric oxide for</p> <p>16 arterial hypertension.</p> <p>17 Q. Would you consider this a review article?</p> <p>18 A. Yes.</p> <p>19 Q. Fair to say that this is a review of the</p> <p>20 work that had been done up until 2012 regarding the</p> <p>21 use of pulsed NO for the treatment of pulmonary</p> <p>22 arterial hypertension?</p> <p>23 A. Yes.</p> <p>24 Q. I believe, you can tell me if I'm wrong,</p> <p>25 but I believe you reproduced Figure 2 from this</p>

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<p>157</p> <p>1 article in paragraph 148 of your declaration; is that</p> <p>2 correct?</p> <p>3 A. Yes.</p> <p>4 Q. Okay. I'd like to turn to Table 1 on the</p> <p>5 next page, which is page 142?</p> <p>6 A. Okay.</p> <p>7 Q. There's a heading here that says, "clinical</p> <p>8 application of inhaled nitric oxide for long-term</p> <p>9 treatment of PAH." Do you see that?</p> <p>10 A. Yes.</p> <p>11 Q. And you say here, "long-term or greater</p> <p>12 than one month pulsed INO dosing appears to favorably</p> <p>13 affect pulmonary hemodynamics findings which with</p> <p>14 other types of therapy appear to correlate with</p> <p>15 benefit." Citation to Table 1. Did I get that</p> <p>16 right?</p> <p>17 A. Yes.</p> <p>18 Q. Do you see Table 1 underneath that passage?</p> <p>19 A. Yes.</p> <p>20 Q. What does Table 1 depict?</p> <p>21 A. It's a summary of published studies on this</p> <p>22 topic.</p> <p>23 Q. And did you conduct any of those studies?</p> <p>24 A. Yes.</p> <p>25 Q. How many of them?</p>	<p>159</p> <p>1 allow for randomized controlled trials of INO and</p> <p>2 hopefully may lead to broad scale application of INO</p> <p>3 in the treatment of chronic diseases such as PAH."</p> <p>4 Did I get that right?</p> <p>5 A. Yes.</p> <p>6 Q. And here INO refers to inhaled nitric</p> <p>7 oxide?</p> <p>8 A. Yes.</p> <p>9 Q. Were those -- were randomized controlled</p> <p>10 trials of INO and PH ever conducted?</p> <p>11 A. Have been and are also planned in the</p> <p>12 future. So it's still an area that's being studied.</p> <p>13 Q. Okay. In your opinion, doctor, would the</p> <p>14 clinical trial results that you've summarized in this</p> <p>15 review article give pulmonologists a reasonable</p> <p>16 expectation that inhaled NO could be used to treat</p> <p>17 PAH?</p> <p>18 A. Yes.</p> <p>19 Q. Okay. You can put that aside.</p> <p>20 A. I also wanted to just fill in the story. I</p> <p>21 wanted to point out that it's not an available drug</p> <p>22 for treating PAH, or PH of any kind, because it's not</p> <p>23 commercially available for outpatients. If it were,</p> <p>24 I would speculate that people would be using it.</p> <p>25 Yes.</p>
<p>158</p> <p>1 A. One of them.</p> <p>2 Q. Okay. And that's the first listed entry</p> <p>3 from 1996?</p> <p>4 A. Yes.</p> <p>5 Q. Okay. If we go to page 145, please. Do</p> <p>6 you see in the left-hand column there's a heading</p> <p>7 entitled, "conclusions and further directions".</p> <p>8 A. Yes.</p> <p>9 Q. You say here, "in summary, uncontrolled</p> <p>10 observational studies of long-term use greater than</p> <p>11 one month of continuous pulsed INO as monotherapy or</p> <p>12 as part of combination therapy in a total of 14</p> <p>13 patients with PAH across five studies have reported</p> <p>14 no significant adverse offense, no elevated METHV</p> <p>15 levels, and no detectable exhaled or ambient NO or</p> <p>16 NO2." Did I get that right?</p> <p>17 A. Yes.</p> <p>18 Q. Would you say that your conclusions in this</p> <p>19 review article in 2012 regarding the use of pulse</p> <p>20 inhaled nitric oxide for the treatment of PAH were</p> <p>21 positive generally?</p> <p>22 A. Yes.</p> <p>23 Q. And then the final paragraph includes with</p> <p>24 the sentence, "advances in INO gas delivery</p> <p>25 technology and strategy to optimize dosing should</p>	<p>160</p> <p>1 Q. Dr. Channick, the court reporter's handed</p> <p>2 you what's been marked as Exhibit 22?</p> <p>3 (Exhibit 22 marked for identification.)</p> <p>4 Q. This is a press release from Therapeutics</p> <p>5 dated August 7th, 2018. Doctor, have you seen</p> <p>6 Exhibit 22 before?</p> <p>7 A. I haven't seen this exhibit, no.</p> <p>8 Q. Are you familiar with Bellerophon?</p> <p>9 A. Yes.</p> <p>10 Q. What is Bellerophon Therapeutics?</p> <p>11 A. It's a company that is involved with</p> <p>12 inhaled -- with nitric oxide. Gas. It's a</p> <p>13 biotherapeutics company.</p> <p>14 Q. And would you agree that in the years -- in</p> <p>15 the time preceding this press release, Bellerophon</p> <p>16 had conducted a phase 3 study of inhaled nitric oxide</p> <p>17 in PAH?</p> <p>18 A. Yes.</p> <p>19 Q. Are you familiar with that study?</p> <p>20 A. Yes.</p> <p>21 Q. And that was the innovation study?</p> <p>22 A. Correct.</p> <p>23 Q. And if you turn to page 2 of the press</p> <p>24 release, the DMC or data monitoring committee</p> <p>25 recommended that the trial be stopped for futility;</p>

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<p>161</p> <p>1 is that right?</p> <p>2 A. Yes.</p> <p>3 Q. What does it mean when a trial is stopped</p> <p>4 for futility?</p> <p>5 A. It means that the company -- the data</p> <p>6 monitoring board has determined that it's unlikely,</p> <p>7 based on the data to date, that they're going to be</p> <p>8 able to prove their primary endpoint for the study.</p> <p>9 Therefore, they may recommend stopping the study.</p> <p>10 Q. To your knowledge, was this study stopped?</p> <p>11 A. Yes.</p> <p>12 Q. Were you involved in the study in any way?</p> <p>13 A. No. But that does not mean that -- I want</p> <p>14 to be clear, that the drug doesn't work. A negative</p> <p>15 study is a neutral study that failed to prove the</p> <p>16 primary endpoint. It does not mean that some group</p> <p>17 of patients within that study did not benefit, in</p> <p>18 some cases, very greatly. It just is a neutral study</p> <p>19 in that it didn't prove the primary endpoint.</p> <p>20 We're trying to get away from the term</p> <p>21 negative studies and really talk about neutral</p> <p>22 studies. It's a better way to describe. Something</p> <p>23 like this study where they didn't -- it felt unlikely</p> <p>24 they were going to be able to prove their primary</p> <p>25 endpoint.</p>	<p>163</p> <p>1 of your declaration, please. Do you see here that</p> <p>2 above paragraph 143 there's a major heading,</p> <p>3 "Liquidia does not infringe claims 9 through 11 and</p> <p>4 14 of the 327 patent." Do you see that?</p> <p>5 A. Yes.</p> <p>6 Q. You're aware that in addition to those</p> <p>7 claims, UTC has asserted claims 1 and 6 of the 327</p> <p>8 patent against Liquidia; is that correct?</p> <p>9 A. Yes.</p> <p>10 Q. Okay. Did you perform an analysis as to</p> <p>11 whether Liquidia would infringe claims 1 and 6?</p> <p>12 A. I did not.</p> <p>13 Q. So you're not offering any opinions in this</p> <p>14 case, at least as of now, as to the potential</p> <p>15 infringement of claims 1 and 6; is that right?</p> <p>16 A. Yes.</p> <p>17 Q. Okay. And as part of your analysis of</p> <p>18 infringement in this case, you consulted the proposed</p> <p>19 label for Yutrepia; is that correct?</p> <p>20 A. Yes.</p> <p>21 Q. Okay. Let's have a look at that.</p> <p>22 (Exhibit 23 marked for identification.)</p> <p>23 Q. Okay. Dr. Channick, the court reporter's</p> <p>24 handed you what's been marked as Exhibit 25 -- let me</p> <p>25 start again. The court reporter's handed you what's</p>
<p>162</p> <p>1 Q. Okay. So you would characterize a study</p> <p>2 that was stopped for futility to be a neutral study,</p> <p>3 not a negative study; is that right?</p> <p>4 A. Absolutely.</p> <p>5 Q. And what would cause you to characterize</p> <p>6 the study as negative?</p> <p>7 A. I would only call it a negative study -- we</p> <p>8 don't like to use the term negative study in our</p> <p>9 design. If it's harmful, if there's signs of harm,</p> <p>10 then I guess you could say that's negative. But in</p> <p>11 terms of not proving the primary endpoint, it</p> <p>12 basically means you haven't proven the drug doesn't</p> <p>13 work. You just haven't proven it does work. That's</p> <p>14 a neutral study.</p> <p>15 Q. Okay. So are you familiar with RISE-IIP</p> <p>16 study with Riociguat?</p> <p>17 A. Yes.</p> <p>18 Q. And that study was terminated for patient</p> <p>19 harm?</p> <p>20 A. Yes.</p> <p>21 Q. And so you would characterize RISE IIP as a</p> <p>22 negative study?</p> <p>23 A. Again, we can go into semantics. So you</p> <p>24 could call it that. Yes.</p> <p>25 Q. Dr. Channick, I'd like to turn to page 64</p>	<p>164</p> <p>1 been marked as Exhibit 23. This is a document</p> <p>2 bearing Bates Numbers LIQ_PH-ILD_0000896 through 910?</p> <p>3 Dr. Channick, do you recognize Exhibit 23?</p> <p>4 A. Yes.</p> <p>5 Q. What is Exhibit 23?</p> <p>6 A. The proposed Yutrepia label.</p> <p>7 Q. When you say, "proposed Yutrepia label", do</p> <p>8 you understand this to be the package insert or</p> <p>9 highlights of prescribing information that would be</p> <p>10 provided with Yutrepia to the extent that it is</p> <p>11 approved and sold in the United States?</p> <p>12 A. Yes.</p> <p>13 Q. Okay. If you could turn to the page ending</p> <p>14 906, please.</p> <p>15 A. Okay.</p> <p>16 Q. Do you see here there's Section 14.2</p> <p>17 entitled, "Pulmonary Hypertension associated with</p> <p>18 IOVWO group 3"?</p> <p>19 A. Yes.</p> <p>20 Q. And then do you see that there's a</p> <p>21 discussion of the INCREASE trial that follows?</p> <p>22 A. Yes.</p> <p>23 Q. And the INCREASE trial is the clinical</p> <p>24 trial that we discussed as part of the Waxman</p> <p>25 publication, Exhibit 15; right?</p>

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<p>165</p> <p>1 A. Yes.</p> <p>2 Q. Okay. Do you have an understanding as to</p> <p>3 why Liquidia cited the INCREASE trial in its proposed</p> <p>4 label for Yutrepia?</p> <p>5 A. No.</p> <p>6 Q. In its proposed label for Yutrepia, does</p> <p>7 Liquidia cite any clinical trial showing the use of</p> <p>8 Yutrepia for the treatment of PHILD?</p> <p>9 MR. SUKDUANG: Objection. Vague.</p> <p>10 THE WITNESS: Ask that question again.</p> <p>11 Q. Sure. So INCREASE was a trial of Tyvaso</p> <p>12 and PHILD patients; right?</p> <p>13 A. Yes.</p> <p>14 Q. Is there any clinical data in this Yutrepia</p> <p>15 label, Exhibit 23, that discusses the use of Yutrepia</p> <p>16 specifically in PHILD patients?</p> <p>17 A. No.</p> <p>18 Q. So the only information in this label</p> <p>19 regarding the use of treprostinil in PHILD patients</p> <p>20 is this discussion of the INCREASE study; correct?</p> <p>21 A. And Triumph study as well. So I guess not</p> <p>22 correct.</p> <p>23 Q. Okay. Triumph is referred to in</p> <p>24 Exhibit 14.1; correct? Section 14.1. I apologize?</p> <p>25 A. Yes.</p>	<p>167</p> <p>1 A. Yes, with the caveat about Triumph and not</p> <p>2 Tyvaso at the time.</p> <p>3 Q. Fair enough. Now, you agree that as part</p> <p>4 of INCREASE, one of the data points that came out of</p> <p>5 INCREASE was a statistically significant INCREASE in</p> <p>6 percent FVC predicted; correct?</p> <p>7 A. Yes, that was the 1.1 percent that we</p> <p>8 talked about earlier. That is correct.</p> <p>9 Q. And if we dig down, and I'm happy to go</p> <p>10 through that exhibit with you in more detail, but in</p> <p>11 certain -- strike that. If you took the general</p> <p>12 population of INCREASE and you cut it down into</p> <p>13 patients with particularly severe disease, they</p> <p>14 showed statistically significant increases in</p> <p>15 absolute FVC; is that right?</p> <p>16 A. Yes.</p> <p>17 Q. Okay. Now, you've offered the opinion, and</p> <p>18 feel free to consult your declaration, that Yutrepia</p> <p>19 will not infringe claims 9 and 10 of the 327 patent</p> <p>20 because there is no mention of FVC in the Yutrepia</p> <p>21 label; is that correct?</p> <p>22 A. Yes.</p> <p>23 Q. Is it your understanding that if</p> <p>24 particular -- if a particular parameter is not</p> <p>25 expressly disclosed in a label, there can be no</p>
<p>166</p> <p>1 Q. Okay. It's under the heading, pulmonary</p> <p>2 arterial hypertension WO group 1"; is that right?</p> <p>3 A. Yes.</p> <p>4 Q. Okay. And what medication is being studied</p> <p>5 in Triumph?</p> <p>6 A. Inhaled treprostinil.</p> <p>7 Q. Which company sponsored Triumph?</p> <p>8 A. United Therapeutics.</p> <p>9 Q. So was it -- strike that. Was it the</p> <p>10 Tyvaso dosage form that was being studied in Triumph?</p> <p>11 A. It wasn't Tyvaso, because this was a</p> <p>12 pre-approval study.</p> <p>13 Q. Sure. What became Tyvaso; is that fair?</p> <p>14 A. I believe so, yes.</p> <p>15 Q. Okay. So let me ask you the question</p> <p>16 again. Aside from the Triumph study with Tyvaso and</p> <p>17 the INCREASE study with Tyvaso -- I'll start again.</p> <p>18 You were correct. If we exclude Triumph -- the</p> <p>19 Triumph study, which was conducted with what became</p> <p>20 Tyvaso, as well as the INCREASE study which was</p> <p>21 conducted with Tyvaso, is there any other clinical</p> <p>22 data reported in the label?</p> <p>23 A. No.</p> <p>24 Q. So the only clinical data that's reported</p> <p>25 in the Yutrepia label is data for Tyvaso; correct?</p>	<p>168</p> <p>1 induced infringement?</p> <p>2 MR. SUKDUANG: Objection to the extent</p> <p>3 you're calling for a legal conclusion.</p> <p>4 Q. I'll rephrase. When you conducted your</p> <p>5 analysis regarding the infringement of the 327</p> <p>6 patent, was it your understanding for purposes of</p> <p>7 that analysis, that if FVC did not expressly appear</p> <p>8 in the Yutrepia label, there could be no infringement</p> <p>9 of claims 9 and 10?</p> <p>10 MR. SUKDUANG: Calls for a legal</p> <p>11 conclusion.</p> <p>12 THE WITNESS: Yeah, I think that's beyond</p> <p>13 my expertise. That specific technical question.</p> <p>14 Q. Well, you've given an opinion here that</p> <p>15 Yutrepia does not infringe?</p> <p>16 A. On FVC.</p> <p>17 Q. On FVC for claims 9 and 10; right?</p> <p>18 A. Yes.</p> <p>19 Q. You agree that the INCREASE study is cited</p> <p>20 in the label for Yutrepia?</p> <p>21 A. Correct.</p> <p>22 Q. And you agree that in the publication of</p> <p>23 the INCREASE study FVC was discussed; correct?</p> <p>24 A. Yes.</p> <p>25 Q. But your opinion is that there is no</p>

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<p>179</p> <p>1 infringement because that data was not specifically</p> <p>2 reproduced in the Yutrepia label; is that correct?</p> <p>3 A. Yes. So therefore, there was no</p> <p>4 instruction regarding FVC in the label.</p> <p>5 Q. Does Yutrepia's label instruct physicians</p> <p>6 to review the data from the INCREASE study?</p> <p>7 A. No. Instruct meaning it shows the data</p> <p>8 that they showed in the label.</p> <p>9 Q. It shows some of the data?</p> <p>10 A. It shows some of the data, correct.</p> <p>11 Q. If you could -- now, you also assessed the</p> <p>12 validity of claims 9 and 10; correct?</p> <p>13 A. Yes.</p> <p>14 Q. Okay. Let me just find this. Let me find</p> <p>15 the right paragraph. Let's turn to paragraph 133,</p> <p>16 please. I may have pointed to the wrong paragraph.</p> <p>17 Let's stick with 133 for now. You've offered the</p> <p>18 opinion, Doctor, that a person of ordinary skill</p> <p>19 would have been motivated to dose Tyvaso to PHILD</p> <p>20 patients according to the instructions in the 2009</p> <p>21 version of the Tyvaso label; right?</p> <p>22 A. Yes.</p> <p>23 Q. And the dosing between the -- the dosing</p> <p>24 regimen for PAH in 2009 labels is the same as the</p> <p>25 dosing regimen for PHILD in the current label; is</p>	<p>171</p> <p>1 A. I don't remember. Maybe a year ago.</p> <p>2 Q. Okay. And approximately how many times</p> <p>3 have you seen the Yutrepia inhaler?</p> <p>4 A. How many times have I seen the inhaler? I</p> <p>5 don't know. Four, maybe.</p> <p>6 Q. Okay. And in what context did you view the</p> <p>7 Yutrepia inhaler?</p> <p>8 A. I think someone brought it to me just to</p> <p>9 show it to me. One of the medical people at the</p> <p>10 company, presumably.</p> <p>11 Q. And when you say "the company", you mean --</p> <p>12 A. Liquidia.</p> <p>13 Q. Okay. Have you reviewed the Yutrepia</p> <p>14 inhaler in the context of this litigation?</p> <p>15 MR. SUKDUANG: Objection. Vague.</p> <p>16 THE WITNESS: I haven't physically looked</p> <p>17 at it. I remember what it looks like and feels like.</p> <p>18 Q. All right. Let me rephrase. That's a fair</p> <p>19 objection. Since you've been retained in this case,</p> <p>20 have you physically inspected the Yutrepia inhaler?</p> <p>21 A. No.</p> <p>22 Q. Okay. When was the last time you saw it?</p> <p>23 A. Six months ago.</p> <p>24 Q. Okay. Now, your opinion is that there's no</p> <p>25 infringement of claims 11 and 14 through the 327</p>
<p>170</p> <p>1 that correct?</p> <p>2 A. Yes.</p> <p>3 Q. Okay. Now, you've also offered the person</p> <p>4 that were a person of ordinary skill to do that, the</p> <p>5 necessary and inevitable result of that would be</p> <p>6 achievement of the FVC characteristics claimed in</p> <p>7 claims 9 and 10; correct?</p> <p>8 A. Yes.</p> <p>9 Q. So do you also believe that if Yutrepia is</p> <p>10 applied to PHILD patients, they will also see --</p> <p>11 necessarily and inevitably see those same</p> <p>12 improvements in FVC?</p> <p>13 A. Yes.</p> <p>14 Q. Okay. Let's go back to paragraph 146 on</p> <p>15 page 65 of your declaration, please. Paragraph 146</p> <p>16 you say, "Liquidia does not infringe claims 11 and 14</p> <p>17 of the 327 patents because Liquidia's dry powder</p> <p>18 inhaler is not a pulsed inhalation device as required</p> <p>19 by the claims." Did I get that right?</p> <p>20 A. Yes.</p> <p>21 Q. Okay. And you have personally examined</p> <p>22 Liquidia's inhaler?</p> <p>23 A. Yes.</p> <p>24 Q. When was the first time you saw Liquidia's</p> <p>25 inhaler?</p>	<p>172</p> <p>1 patent because that inhaler, the Yutrepia inhaler, is</p> <p>2 not a pulsed inhalation device; is that right?</p> <p>3 A. Correct.</p> <p>4 Q. Okay. And in interpreting what was a</p> <p>5 pulsed inhalation device as required by the claims,</p> <p>6 what meaning did you ascribe to pulsed inhalation</p> <p>7 device. To be clear, I'm not looking for an opinion</p> <p>8 on the meaning of the term. I'm asking what meaning</p> <p>9 you ascribe as part of your analysis?</p> <p>10 MR. SUKDUANG: I understand your caveat,</p> <p>11 but it's the same question. So objection, calls for</p> <p>12 a legal conclusion. You can go ahead and answer, Dr.</p> <p>13 Channick.</p> <p>14 THE WITNESS: What is my understanding of</p> <p>15 what a pulsed inhalation device is?</p> <p>16 Q. Why don't we start there?</p> <p>17 A. I think it's a device that delivers a pulse</p> <p>18 of whatever you're given. In this case, the powder.</p> <p>19 So I mean, what a pulse is, it's an active energy, I</p> <p>20 guess you could say, that delivers a pulse. So</p> <p>21 there's -- for instance, ultrasonic nebulizer. The</p> <p>22 patient generates either a pressure or flow and the</p> <p>23 machine kicks in and gives them a pulse. It gives</p> <p>24 them a breath.</p> <p>25 The system I developed for nitric oxide,</p>

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<p>173</p> <p>1 similar thing, it's a pulse. It's a mechanism by 2 which the patient can basically be delivered a 3 breath. That's what I think about a pulse delivery. 4 Q. And is that the definition that you applied 5 when assessing infringement of claims 11 and 14 of 6 the 327 patent? 7 A. Yes, that was my understanding of what a 8 pulsed device is. 9 Q. Okay. Did you review the specification of 10 the 327 patent in assessing what a pulsed inhalation 11 device might be? 12 A. The specification? 13 Q. Anything in the patent other than the 14 claims? 15 A. I don't know that I saw a definition in the 16 327 patent of what a -- a strict definition of a 17 pulse inhalation device. 18 Q. Okay. In your experience, Doctor, have you 19 encountered a pulse inhalation device that is also a 20 dry powder inhaler? 21 A. No, not in my experience. 22 Q. Could you go to the 327 patent? 23 Exhibit 14. 24 A. Okay. 25 Q. If you could go to column 21 of the 327</p>	<p>175</p> <p>1 with the powder in it that kicks that powder with 2 energy could occur. My understanding is that the 3 device is not a pulsed inhalation device as is 4 described. That's all I can say. 5 Q. And you said you're understanding. What is 6 that understanding based on? 7 A. Well, there's no energy to it. There's no 8 power to it. It's just a little piece of plastic 9 that the patient pulls in, and they get this powder. 10 Like if you sucked it out of a straw, that's not a 11 pulse inhalation device. Just common sense, right? 12 Q. If you could turn to column 54 of the 327 13 patent. I'd like to look at the claims. 14 A. Okay. 15 Q. Do you see claim 11 around line 50? 16 A. Yes. 17 Q. It says, "the method of claim 1 wherein 18 said administering is performed by a pulse 19 administration device." Did I get that right? 20 A. Yes. 21 Q. Now, let's look at claim 14. It says, "the 22 method of claim 11 wherein the pulsed inhalation 23 device is a dry powder inhaler comprising 24 treprostinil or a pharmaceutically acceptable salt 25 thereof." Did I get that right?</p>
<p>174</p> <p>1 patent, please. 2 A. Okay. 3 Q. Let's go to line 6, please. Are you there? 4 A. Yup. 5 Q. It says, "in some embodiments, the 6 inhalation device, such as a pulsed inhalation 7 device, may be a dry powder inhaler, which may 8 contain a dry power composition or formulation 9 causing treprostinil, its pro drug, its 10 pharmaceutically acceptable salt, or a 11 pharmaceutically acceptable salt of its pro drug." 12 Did I get that right? 13 A. Yes. 14 Q. So do you agree that the 327 patent allows 15 for a dry powder inhaler to be a pulsed inhalation 16 device? 17 MR. SUKDUANG: Objection. Vague. 18 THE WITNESS: They're not defining what a 19 pulsed inhalation device is here. They say such as a 20 pulsed inhalation device. I guess that's vague to 21 me, what they mean by some embodiments. Such as a 22 pulsed inhalation device might be a dry powder 23 inhaler. To me it seems like, theoretically a pulsed 24 inhalation device could contain a dry powder inhaler. 25 In other words, you can have an electronic machine</p>	<p>176</p> <p>1 A. Yes. 2 Q. Does this indicate to you that the 3 inventors of the 327 patent intended to define a dry 4 powder inhaler as a subset of a post inhalation? 5 MR. SUKDUANG: Objection. Mischaracterizes 6 the claim. Calls for claim construction. 7 Foundation. 8 THE WITNESS: I honestly don't know. I 9 mean, I know that I disagree. The Yutrepia device is 10 not a pulsed inhalation device. So I don't -- the 11 device that is currently used for the dry powder 12 inhaler for Tyvaso, I don't believe is a pulsed 13 inhaler device. I know that the Yutrepia device is 14 not a pulsed inhalation device as I understand it. 15 Q. Okay. Let's look up at claim 1, if you 16 don't mind. Line 6 of column 54. 17 A. Okay. 18 Q. Do you see that there's a term in claim 1, 19 "effective amount"? 20 A. Yes. 21 Q. In assessing infringement and invalidity of 22 this claim, what meaning did you ascribe to 23 "effective amount"? 24 MR. SUKDUANG: Objection to the extent 25 you're calling for a claim construction and legal</p>

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<p>177</p> <p>1 conclusion. Go ahead.</p> <p>2 THE WITNESS: Tell you what. We're not</p> <p>3 dealing with infringement of one.</p> <p>4 Q. Strike that. You offered an invalidity</p> <p>5 opinion of claim 1; correct?</p> <p>6 A. Correct.</p> <p>7 Q. And in order to understand what claim 1</p> <p>8 covers; right?</p> <p>9 A. Yes.</p> <p>10 Q. Okay. And in understanding what claim 1</p> <p>11 covers, what meaning did you ascribe to effective</p> <p>12 amount?</p> <p>13 MR. SUKDUANG: Objection to the extent</p> <p>14 you're calling for a legal conclusion. You can go</p> <p>15 ahead and answer.</p> <p>16 THE WITNESS: A dose that will have an</p> <p>17 effect.</p> <p>18 Q. And what effect is that?</p> <p>19 A. Method for improving exercise capacity in a</p> <p>20 patient having Pulmonary Hypertension associated with</p> <p>21 interstitial lung disease is what claim 1 says.</p> <p>22 Q. Okay. So the effect is the improvement in</p> <p>23 exercise capacity in a PHILD patient?</p> <p>24 A. In claim 1, yes.</p> <p>25 Q. Okay. So to your understanding, does claim</p>	<p>179</p> <p>1 a statistically significant reduction of at least one</p> <p>2 exacerbations of the interstitial lung disease?</p> <p>3 A. Yes.</p> <p>4 Q. When assessing the validity of claim 6,</p> <p>5 what meaning did you ascribe to statistically</p> <p>6 significant?</p> <p>7 MR. SUKDUANG: Objection to the extent it</p> <p>8 calls for a legal conclusion. You can go ahead and</p> <p>9 answer.</p> <p>10 THE WITNESS: I think I described what the</p> <p>11 accepted statistical significance is with the P value</p> <p>12 of less than .05.</p> <p>13 Q. Is it possible to have a statistically</p> <p>14 significant result with a single patient?</p> <p>15 A. In general, no.</p> <p>16 Q. Why not?</p> <p>17 A. It's statistics. I mean -- obviously, the</p> <p>18 more patients you study the more power you have to</p> <p>19 show real differences versus non-real differences or</p> <p>20 coincidences. Chance.</p> <p>21 Q. Sure. Just so I understand, when you say</p> <p>22 "no" you're referring to a single administration</p> <p>23 event to a single patient; right?</p> <p>24 A. What do you mean?</p> <p>25 MR. SUKDUANG: Objection. Vague and</p>
<p>178</p> <p>1 I require that the method of treatment be performed</p> <p>2 with the intention of improving exercise capacity in</p> <p>3 a PHILD patient?</p> <p>4 MR. SUKDUANG: Objection. Vague and object</p> <p>5 to the extent it calls for a legal conclusion.</p> <p>6 THE WITNESS: The intention? You mean from</p> <p>7 a validity legal point of view, or as a clinician</p> <p>8 using the drug on a patient.</p> <p>9 Q. I'm asking you as a clinician. You said</p> <p>10 that you meet the requirement for person of ordinary</p> <p>11 skill in the art.</p> <p>12 A. Yes.</p> <p>13 Q. I'm asking you, as you read this claim --</p> <p>14 A. I would expect the drug to improve exercise</p> <p>15 capacity, yes.</p> <p>16 Q. Okay. So improvement of exercise capacity</p> <p>17 is a requirement of claim 1?</p> <p>18 A. I would expect to see an improvement in</p> <p>19 exercise capacity, yes.</p> <p>20 MR. SUKDUANG: I would object it calls for</p> <p>21 a legal conclusion and claim construction.</p> <p>22 Q. Let's look at claim 6 which you performed</p> <p>23 an invalidity analysis of. Are you there?</p> <p>24 A. Yes.</p> <p>25 Q. Do you see here that there's a reference to</p>	<p>180</p> <p>1 mischaracterizes your question.</p> <p>2 Q. Let me backup. I'm not sure how I can --</p> <p>3 MR. SUKDUANG: Mischaracterized your prior</p> <p>4 question.</p> <p>5 Q. Let me try again. If I dosed a patient</p> <p>6 with a drug multiple times, theoretically, could I</p> <p>7 get statistical significance from the course of</p> <p>8 multiple dosing in a single patients?</p> <p>9 A. It depends what you were measuring. If</p> <p>10 you're measuring an effect that you see after each</p> <p>11 dose, you could say that that measurement -- if you</p> <p>12 repeat the measurement, then you could -- then that</p> <p>13 increases the power. Because then you're not doing</p> <p>14 it on multiple patients. You're doing multiple</p> <p>15 measurements on the same patient.</p> <p>16 Q. So yes, multiple measurements in one</p> <p>17 patient theoretically could lead to statistical</p> <p>18 significance?</p> <p>19 A. Well, it depends on the significance of</p> <p>20 what. You could say --</p> <p>21 Q. I agree. A single data point from a single</p> <p>22 data patient cannot have statistical significance, in</p> <p>23 your opinion?</p> <p>24 A. Correct.</p> <p>25 Q. Okay. Dr. Channick, could you pull out</p>

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<p>181</p> <p>1 Exhibit 20, if you don't mind?</p> <p>2 A. Sure.</p> <p>3 Q. And this is the Saggar 2014 reference that</p> <p>4 we were discussing earlier; right?</p> <p>5 A. Yes.</p> <p>6 Q. And this is a study of 15 patients that</p> <p>7 were administered parenteral treprostinil; is that</p> <p>8 right?</p> <p>9 A. Yes.</p> <p>10 Q. With apologies to your counsel, I realized</p> <p>11 I forgot to ask you about the conclusion of this</p> <p>12 study. That begins at page 128 and goes onto</p> <p>13 page 129?</p> <p>14 MR. SUKDUANG: Why are you apologizing to</p> <p>15 me?</p> <p>16 MR. ROMEO: Because you asked if I was done</p> <p>17 with the reference before we took a break and I</p> <p>18 thought I was. I realized I was not. I like to keep</p> <p>19 my promises if I can.</p> <p>20 MR. SUKDUANG: I've learned to believe that</p> <p>21 that's never the case. That's not a negative comment</p> <p>22 on you, just lawyers in general.</p> <p>23 THE WITNESS: Okay.</p> <p>24 Q. So the conclusion which begins on page 128</p> <p>25 reads, "this open label study suggests that gradual</p>	<p>183</p> <p>1 not to get too deep into. We have a therapy that's</p> <p>2 available that he helps these patients with pulmonary</p> <p>3 fibrosis and Pulmonary Hypertension, and continue to</p> <p>4 be used in those patients effectively. There has not</p> <p>5 been a randomized and controlled parenteral</p> <p>6 treprostinil. So the hypothesis generation is a</p> <p>7 valid conclusion. But it doesn't pro-include using</p> <p>8 the drug in an effective way as it has been used and</p> <p>9 as it continues to be used.</p> <p>10 Q. We talked a lot today -- let me ask you the</p> <p>11 question again slightly differently. We've used the</p> <p>12 phrase, POSA or person of ordinary skill in the art,</p> <p>13 a number of times today. In your opinion, how would</p> <p>14 a person of ordinary skill in the art read a</p> <p>15 statement that these findings are only hypothesis</p> <p>16 generating and require confirmation in a multiple</p> <p>17 center randomized study?</p> <p>18 A. I couldn't give you an answer on how a</p> <p>19 person would read that particular statement other</p> <p>20 than how it was made in what context with what</p> <p>21 article and what findings. If you pulled that</p> <p>22 sentence out with literally no context, then you</p> <p>23 might have one conclusion. If you put it at the end</p> <p>24 of a study showing a very robust effect of a</p> <p>25 treatment, they're going to have a different</p>
<p>182</p> <p>1 initiation and chronic administration of parenteral</p> <p>2 treprostinil therapy may improve hemodynamics and</p> <p>3 right heart function without compromising systemic</p> <p>4 oxygenation in an advanced PH phenotype with RV in</p> <p>5 the setting of PF. These findings are only</p> <p>6 hypothesis generating and require confirmation in a</p> <p>7 multicenter randomized study design."</p> <p>8 Did I read that correctly?</p> <p>9 A. Yes.</p> <p>10 Q. What does it mean for findings to be only</p> <p>11 hypothesis generating?</p> <p>12 A. Well, that's an opinion. There's not a</p> <p>13 specific meaning. It depends on, you know, what</p> <p>14 you're talking about. So it's hypothesis generating.</p> <p>15 I don't want to speak for what these authors meant by</p> <p>16 hypothesis generating. Sometimes we see, you know a</p> <p>17 study -- for instance, if you're trying to get a</p> <p>18 label from the FDA and have you a phase 2 study or an</p> <p>19 uncontrolled study that shows a he benefit, you can</p> <p>20 say, well, now we need to do a larger, randomized</p> <p>21 trial to prove that to the satisfaction, let's say,</p> <p>22 to gate label extension or get an indication.</p> <p>23 I mean, that could be one meaning.</p> <p>24 Certainly if it relates to if you see an effect, that</p> <p>25 may translate into what you do. We have -- again,</p>	<p>184</p> <p>1 conclusion.</p> <p>2 Q. Okay. So in your opinion, what would a</p> <p>3 POSA take from this conclusion as it relates to the</p> <p>4 results that are reported in the Saggar 2014?</p> <p>5 A. They would probably take what I just</p> <p>6 explained. That this was an effective treatment that</p> <p>7 was used in real world studies by these finances, and</p> <p>8 used by many other physicians. But if one was to do</p> <p>9 a -- wanted to do a phase 3 study to see if you could</p> <p>10 get approval, then you might do that. That's</p> <p>11 hypothesis generating.</p> <p>12 So other than that, I can only state what I</p> <p>13 take from it.</p> <p>14 Q. Okay. Can we go off the record for a</p> <p>15 minute, please?</p> <p>16 VIDEOGRAPHER: We're going off the record.</p> <p>17 The time is 3:14.</p> <p>18 (Recess taken.)</p> <p>19 VIDEOGRAPHER: We're back on the record.</p> <p>20 It's 3:25 P.M.</p> <p>21 MR. HOROWITZ: Dr. Channick, thank you for</p> <p>22 your time today. At this time, United Therapeutics</p> <p>23 has no further questions for you.</p> <p>24 THE WITNESS: Thank you.</p> <p>25 MR. SUKDUANG: I have a couple questions.</p>

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<p>185</p> <p>1 EXAMINATION BY MR. SUKDUANG</p> <p>2 Q. Do you have Exhibit 1, which I believe is</p> <p>3 your expert report?</p> <p>4 A. Yes.</p> <p>5 Q. And can you go to page 48?</p> <p>6 A. Okay.</p> <p>7 Q. Page 48. There's a section D titled, "2017</p> <p>8 INCREASE study description discloses claims 1, 6, and</p> <p>9 9 through 11 of the 327 patent." Did I read that</p> <p>10 correctly?</p> <p>11 A. Yes.</p> <p>12 Q. And does section D span paragraph 107</p> <p>13 through 110?</p> <p>14 A. Yes.</p> <p>15 Q. Now, do you remember being asked questions</p> <p>16 today regarding the 2017 INCREASE study description?</p> <p>17 A. Yes.</p> <p>18 Q. And do you recall being asked questions by</p> <p>19 counsel as to whether the 2017's INCREASE study</p> <p>20 description had slight differences between the</p> <p>21 INCREASE New England journal of medicine paper in</p> <p>22 terms of inclusion/exclusion criteria?</p> <p>23 MR. ROMEO: Object to form.</p> <p>24 THE WITNESS: Yes.</p> <p>25 Q. Do those slight differences change the</p>	<p>187</p> <p>1 Q. Do you think the CEO of United Therapeutics</p> <p>2 would misrepresent data in earnings calls to her</p> <p>3 shareholders?</p> <p>4 A. No.</p> <p>5 MR. ROMEO: Object to form.</p> <p>6 Q. Counsel did not direct to you portions of</p> <p>7 Dr. Rothblatt's actual statements to shareholders,</p> <p>8 did he?</p> <p>9 A. No.</p> <p>10 Q. Can you go to page 10 of this document,</p> <p>11 please?</p> <p>12 A. Okay.</p> <p>13 Q. I understand it's a long paragraph that's</p> <p>14 not numbered, but in the top third, I'm going to have</p> <p>15 you read it to yourself. But there's a sentence that</p> <p>16 begins, having said that, both through the effort of</p> <p>17 our medical affairs group. Do you see that?</p> <p>18 A. I'm looking for it.</p> <p>19 Q. It's about 8 lines down.</p> <p>20 A. There it is.</p> <p>21 Q. If you could read starting 8 lines down</p> <p>22 through to about line 15. Just read it to yourself</p> <p>23 and let me know when you're finished.</p> <p>24 A. I'm finished.</p> <p>25 Q. Okay. In this section, is Dr. Rothblatt</p>
<p>186</p> <p>1 opinion you've provided in your declaration?</p> <p>2 MR. ROMEO: Objection to form.</p> <p>3 THE WITNESS: No.</p> <p>4 Q. Can you pull out number 18? Exhibit 18.</p> <p>5 A. Okay.</p> <p>6 Q. Do you recall being asked questions</p> <p>7 regarding Exhibit 18 today?</p> <p>8 A. Yes.</p> <p>9 Q. And Exhibit 18, just for the record, is the</p> <p>10 May 2nd, 2018, FQ12018 earnings call from United</p> <p>11 Therapeutics; is that correct?</p> <p>12 A. Yes.</p> <p>13 Q. Counsel asked you questions today regarding</p> <p>14 doctor -- let me rephrase. Do you recall counsel</p> <p>15 asking you questions today regarding whether Dr.</p> <p>16 Rothblatt was a medical doctor?</p> <p>17 A. He asked what kind of doctorate she had.</p> <p>18 Q. Okay. Do you understand Dr. Rothblatt is</p> <p>19 the CEO of United Therapeutics?</p> <p>20 A. Yes.</p> <p>21 MR. ROMEO: Object to form.</p> <p>22 Q. Do you think the CEO of United Therapeutics</p> <p>23 would lie to shareholders?</p> <p>24 MR. ROMEO: Object to form.</p> <p>25 THE WITNESS: Presumably no.</p>	<p>188</p> <p>1 discussing WHO group 3 patients?</p> <p>2 MR. ROMEO: Object to form.</p> <p>3 THE WITNESS: Yes.</p> <p>4 Q. And would that include PHILD patients?</p> <p>5 MR. ROMEO: Same objection.</p> <p>6 THE WITNESS: Yes.</p> <p>7 Q. And does it indicate -- did Dr. Rothblatt</p> <p>8 tell her shareholders that there were unmistakable</p> <p>9 signals that some of the leading finances in this</p> <p>10 field saw?</p> <p>11 MR. ROMEO: Same objection.</p> <p>12 THE WITNESS: Yes.</p> <p>13 Q. Do you agree that as of 2018, there were</p> <p>14 unmistakable signals that inhaled treprostinil would</p> <p>15 work in PHILD patients?</p> <p>16 MR. ROMEO: Object to form.</p> <p>17 THE WITNESS: Yes.</p> <p>18 Q. Okay. And counsel asked you questions</p> <p>19 about Dr. Rothblatt, but in this section that counsel</p> <p>20 did not point you to, does Dr. Rothblatt point out</p> <p>21 clinicians that provide this opinion?</p> <p>22 MR. ROMEO: Object to form.</p> <p>23 THE WITNESS: Yes.</p> <p>24 Q. And who was one of the clinicians that</p> <p>25 supported Dr. Rothblatt's statements to her</p>

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<p>189</p> <p>1 shareholders?</p> <p>2 MR. ROMEO: Object to form.</p> <p>3 THE WITNESS: Well, she mentioned Dr.</p> <p>4 Waxman.</p> <p>5 Q. Is that the Dr. Waxman that we've been</p> <p>6 discussing earlier today?</p> <p>7 A. Yes.</p> <p>8 Q. Okay. You see there's a sentence that</p> <p>9 says, "I called out one of them on the call, Dr.</p> <p>10 Waxman, but there are many others who said to U T,</p> <p>11 quote, this drug works. Close quote." Do you see</p> <p>12 that?</p> <p>13 A. Yes.</p> <p>14 Q. Do you see the phrase, quote "this drug</p> <p>15 works"?</p> <p>16 A. Yes.</p> <p>17 Q. Does that -- what does the quotations</p> <p>18 around that phrase indicate to you?</p> <p>19 MR. ROMEO: Object to form.</p> <p>20 THE WITNESS: That was Dr. Waxman's quote</p> <p>21 about inhaled treprostinil in group 3 patients.</p> <p>22 Q. Okay. And that was back in 2018?</p> <p>23 A. Yes.</p> <p>24 Q. Could you pull out number 20, which I think</p> <p>25 is the Saggar 2014 paper?</p>	<p>191</p> <p>1 Did counsel put in front of you any paper from any</p> <p>2 time using treprostinil in any manner that indicated</p> <p>3 it would not work for PHILD?</p> <p>4 MR. ROMEO: Object to form.</p> <p>5 THE WITNESS: No.</p> <p>6 Q. In the course of your career are you aware</p> <p>7 of any paper reporting any results of inhaled</p> <p>8 treprostinil not working for PHILD patients?</p> <p>9 MR. ROMEO: Object to form.</p> <p>10 THE WITNESS: No.</p> <p>11 Q. You're a consultant in the -- you've</p> <p>12 consulted for United Therapeutics in the past?</p> <p>13 A. Yes.</p> <p>14 Q. Do you know why United Therapeutics have</p> <p>15 consulted with you in the past?</p> <p>16 MR. ROMEO: Object to form.</p> <p>17 THE WITNESS: Providing expert opinion and</p> <p>18 advice to the company.</p> <p>19 Q. Okay. In your experience, would United</p> <p>20 Therapeutics hire you as a consultant if they didn't</p> <p>21 think your opinions were valid and verifiable?</p> <p>22 MR. ROMEO: Object to form.</p> <p>23 THE WITNESS: I would presume not.</p> <p>24 MR. SUKDUANG: No further questions.</p> <p>25 MR. ROMEO: Nothing further from United</p>
<p>190</p> <p>1 A. Okay.</p> <p>2 Q. Do you have that in front of you?</p> <p>3 A. Yes.</p> <p>4 Q. Could you go to internal page 129? It ends</p> <p>5 in 232. Are you there?</p> <p>6 A. Yes.</p> <p>7 Q. Do you see a section titled, "funding"?</p> <p>8 A. Yes.</p> <p>9 Q. And where did the funding for the Saggar</p> <p>10 paper come from?</p> <p>11 A. Both the National Heart Lung and Blood</p> <p>12 institute and the United Therapeutics company.</p> <p>13 Q. And do you understand that the United</p> <p>14 Therapeutics is the UTC that is the company asserting</p> <p>15 the 327 patent?</p> <p>16 MR. ROMEO: Object to form.</p> <p>17 THE WITNESS: Yes.</p> <p>18 Q. Okay. Counsel also talked to you today</p> <p>19 regarding Riociguat. Do you recall those questions?</p> <p>20 A. Yes.</p> <p>21 Q. And counsel also talked to you, I think,</p> <p>22 today about inhaled nitric oxide. Do you remember</p> <p>23 those questions?</p> <p>24 A. Nitric oxide.</p> <p>25 Q. We're not blowing up cars here, I guess.</p>	<p>192</p> <p>1 Therapeutics.</p> <p>2 VIDEOGRAPHER: This concludes today's</p> <p>3 deposition. We're going off the record. The time is</p> <p>4 3:35 P.M.</p> <p>5 (Recess taken.)</p> <p>6 MR. SUKDUANG: I need a daily rough today</p> <p>7 and an expedited final.</p> <p>8 MR. ROMEO: Same from us.</p> <p>9 (Proceedings concluded at 3:35 P.M.)</p> <p>10</p> <p>11</p> <p>12</p> <p>13</p> <p>14</p> <p>15</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p>

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<p>193</p> <p>1 DECLARATION UNDER PENALTY OF PERJURY</p> <p>2</p> <p>3 I, DR. RICHARD CHANNICK, do hereby certify</p> <p>4 under penalty of perjury that I have read the</p> <p>5 foregoing transcript of my deposition taken April 6,</p> <p>6 2024; that I have made such corrections as appear</p> <p>7 noted on the Deposition Errata Page attached hereto</p> <p>8 and signed by me; that my testimony as contained</p> <p>9 herein, as corrected, is true and correct.</p> <p>10</p> <p>11 Dated this ____ day of _____,</p> <p>12 2024, at _____,</p> <p>13 California.</p> <p>14</p> <p>15 _____</p> <p>16 DR. RICHARD CHANNICK</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p>	
<p>194</p> <p>1 STATE OF CALIFORNIA)</p> <p>2)</p> <p>3 COUNTY OF LOS ANGELES)</p> <p>4</p> <p>5 I, Michael Cagliata, Certified</p> <p>6 Shorthand Reporter No. 14491, do hereby</p> <p>7 Certify:</p> <p>8 That prior to being examined, the witness</p> <p>9 named in the foregoing deposition was by me duly</p> <p>10 sworn to testify the truth, the whole truth, and</p> <p>11 nothing but the truth;</p> <p>12 That said deposition was taken down by me</p> <p>13 in shorthand and thereafter reduced to print by</p> <p>14 means of computer-aided transcription; and the same</p> <p>15 is a true, correct, and complete transcript of said</p> <p>16 proceedings.</p> <p>17 I further certify that I am not</p> <p>18 interested In the outcome of the action.</p> <p>19 Witness my hand this 6th day of April, 2024.</p> <p>20</p> <p>21 <i>M. Cagliata</i></p> <p>22 _____</p> <p>23 Michael Cagliata, CSR #14491, RPR</p> <p>24 Certified Shorthand Reporter</p> <p>25 In and for the State of California</p>	

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EXHIBIT 24

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August 2, 2024

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Re: *United Therapeutics Corporation v. Liquidia Technologies, Inc.*, C.A. No. 23-975

Dear Counsel:

We write on behalf of Defendant Liquidia Technologies, Inc. (“Liquidia”) to respond to Plaintiff United Therapeutics Corporation’s (“UTC”) letter dated July 17, 2024 (“Letter”). UTC took issue with certain of Liquidia’s objections and responses to UTC’s First Set of Requests for Production of Documents and Things (Nos. 1-17) (“RFPs”). Below, Liquidia addresses UTC’s comments in its Letter.

Liquidia’s General Objections Relating to “NDA No. 213005” and “Liquidia’s NDA”

Liquidia is not withholding otherwise responsive documents based on UTC’s definition of “NDA No. 213005” and “Liquidia’s NDA.”

Liquidia Stated In Its Responses and Objections that It Will Produce Documents On A Rolling Basis



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UTC argues in its Letter that “Liquidia’s reference to its ‘core technical document production’ is insufficient for UTC RFP Nos. 1-3, 7, and 10, and that those RFPs are not addressed by Liquidia’s April 8, 2024 production. Liquidia disagrees and points UTC to its own RFP responses, which directed Liquidia to documents that UTC had previously produced. Nonetheless, in each of UTC RFP Nos. 1-3, 7 and 10, Liquidia had agreed to produce responsive documents consistent with Liquidia’s objections.

For **UTC RFP No. 1**, Liquidia is not withholding otherwise responsive documents based on UTC’s definition of “NDA No. 213005” and “Liquidia’s NDA.”

For **UTC RFP No. 2**, Liquidia has already produced its correspondence with the FDA and has indicated in its response that it will produce such documents on a rolling basis. As stated in its response, Liquidia will withhold any correspondence with the FDA to the extent it is privileged or not relevant to the claims or defenses in this litigation.

For **UTC RFP No. 7**, all claims of the asserted patent require improvement of exercise capacity, as they depend directly or indirectly from claim 1. As such, Liquidia’s objections are proper. Further, pre-clinical studies and trials do not involve administration to a patient as required by your RFP, so we are not withholding any responsive pre-clinical documents. Clinical studies are not relevant to infringement due to the safe harbor provisions afforded by the Hatch-Waxman Act, nor are they relevant to willfulness and damages as UTC suggests, albeit without any explanation or support, because no sales have occurred and because of the safe harbor provisions. Nonetheless, to the extent Liquidia is in possession of documents responsive to UTC RFP No. 7, it will include such studies addressing the outcomes identified in UTC RFP No. 7.

For **UTC RFP No. 10**, it is unclear to Liquidia how comparisons between Yutrepia® and treprostinil products that do not relate to “patients with PH-ILD” would be relevant to the claims and defenses in this case, which are expressly limited to PH-ILD, and UTC has provided no explanation as to their relevance. Under the Acts Giving Rise to This Action section, UTC’s First Amended Complaint lists and describes Liquidia’s amendment to NDA No. 213005, which adds PH-ILD as an indication. D.I. 8, ¶18. UTC does not assert any patent that does not relate to “patients with PH-ILD,” and UTC has dropped its allegations with respect to the ’793 patent. Further, UTC’s allegations that comparisons of Yutrepia® to other products for indications other than PH-ILD are relevant to issues concerning competition in the marketplace, trial and failure, and whether Liquidia “markets and sells Yutrepia®” to or for Group 3 patients similarly lacks merit. The only relevant issue is how Yutrepia® will compete in the marketplace for PH-ILD, as that is the limited scope of the ’327 patent claims. Whether others tried and failed to administer drugs for exercise capacity is also not relevant as it is not limited to PH-ILD patients as the claims require. As such, Liquidia stands by its response to RFP No. 10 and will produce documents in accordance with Liquidia’s objections and response.



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Liquidia's Relevance-Based Withholding Is Not Improper

Rule 26 of the Federal Rules of Civil Procedure limits discovery to documents relevant to the parties claims or defenses and the production of which is proportional to the needs of the case. Here, the asserted patent is limited to PH-ILD patients and thus any infringement and damages UTC claims are directed to that issue. Liquidia has agreed to produce relevant documents.

- **UTC RFP No. 3**

For **UTC RFP No. 3**, Liquidia's response states that it will produce responsive documents on a rolling basis in a timeframe commensurate with the scope of the Request. Liquidia is not withholding documents and will produce its most recent regulatory tracking logs in due course.

- **UTC RFP Nos. 4-6**

Regarding **UTC RFP Nos. 4-6**, Liquidia has not yet launched its Yutrepia® product. To the extent that Yutrepia's launch never happens, the documents sought by UTC RFP Nos. 4-6 are not relevant. Documents and things concerning the decision to launch, launch at risk, or whether or when to launch, as requested by UTC RFP No. 4, are not relevant if Liquidia does not launch. Moreover, and contrary to UTC's assertion that it is entitled to know "when that launch" will happen is incorrect. The Court already denied UTC's preliminary injunction motion, UTC has not sought reconsideration of that decision, and any future launch by Liquidia will be known by UTC. Further, as you are aware, in a separate case filed by UTC, the court ordered the FDA to provide notice to UTC when the FDA intends to issue a decision regarding Yutrepia® approval. Thus, UTC will have adequate notice. If, per UTC's assertion, Liquidia has already infringed by submitting its NDA, UTC already has the relevant information, as Liquidia produced those documents. The desire to know when Yutrepia® may launch is not relevant to this case, but instead designed to permit UTC to use that information to continue its campaign with doctors, patients, payors, and the investing community to disparage the Yutrepia® product.

Documents and things concerning the preparations for manufacture, pre-commercial manufacture, commercial manufacture, or launch, as requested by **UTC RFP No. 5**, are not relevant. Indeed, none of the asserted claims are directed to manufacturing, pre-commercial manufacturing, commercial manufacturing or launch. As such, none of these requested documents are relevant, even upon launch of Yutrepia® and again, are designed only to obtain information to forestall or hinder Liquidia's future launch.

Finally, documents and things sufficient to show third parties who supported or contributed to the preparations for manufacture, pre-commercial manufacture, commercial manufacture, or launch, as requested by **UTC RFP No. 6**, are also not relevant for the same reasons discussed above. Further, UTC admits that its infringement case is based on "**administration** of [Liquidia's] proposed product, Yutrepia®." This admission further confirms that RFP No. 6 seeks irrelevant



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information as third-parties who “supported or contributed to Liquidia’s **preparations for manufacture**” have no bearing on infringement or damages.

To the extent UTC desires to meet and confer to explain why such requests are relevant, Liquidia is willing to confer.

- **UTC RFP No. 9**

Regarding **UTC RFP No. 9**, as explained above in relation to UTC RFP Nos. 4-6, Liquidia’s plans and efforts to market, advertise, and promote administration of Yutrepia® for PH-ILD would not be relevant if Liquidia does not launch. In the event that Liquidia does not launch Yutrepia®, Liquidia would also not market, advertise, and promote the administration of Yutrepia® for PH-ILD.

UTC argues that documents responsive to UTC RFP No. 9 would be relevant to “whether Liquidia will actively induce prescribers and patients to directly infringe the claimed methods of treatment upon launch of Yutrepia (for any indication).” However, such alleged induced infringement will only occur if Liquidia launches Yutrepia®. Moreover, if and when Liquidia does launch Yutrepia®, Liquidia has agreed to produce responsive documents in accordance with its objections and responses that would bear, according to UTC, on the “actively induce” issue.

UTC also argues that documents responsive to UTC RFP No. 9 would be “relevant to UTC’s rebuttal of Liquidia’s invalidity defenses, such as identification of the relevant market and related inquiry of commercial success.” Although it is unclear to Liquidia what exactly UTC’s theory of relevance is, any Liquidia marketing, advertising, or promotional materials would only reflect the relevant market and UTC’s commercial success in the world post-Yutrepia® launch. Any Liquidia marketing, advertising, or promotional materials that UTC receives prior to Yutrepia’s launch would not reflect, and thus not be relevant to, the market and UTC’s alleged commercial success where Yutrepia® does not yet exist.

UTC also argues that the documents sought in RFP No. 9 are relevant to Liquidia’s assertion that it will not usurp sales from UTC but will instead expand the PH-ILD market. Again, any usurpation or sales or expansion of the market has not occurred because Liquidia has not yet launched. Moreover, this issue pertained to UTC’s allegations of irreparable harm in its preliminary injunction motion, which was denied. But again, to the extent Yutrepia® is launched, Liquidia has agreed to produce relevant documents consistent with its objections and responses to RFP No. 9 and other RFPs served by UTC.

UTC asserts that “non-final drafts or versions of responsive documents, such as documents concerning product differentiation, marketing statements, or communications with prescribers or other health care providers” are relevant to Liquidia’s intent to infringe and willfulness. Again, this argument is unripe when the alleged infringing act has not yet occurred. Moreover, other than stating they are relevant, UTC has not provided any basis as to their relevance. Simply stating a



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document is relevant does not make it so. Moreover, with respect to any alleged inducement, Liquidia has already produced its proposed labelling. In the spirit of compromise, Liquidia will also agree to produce final FDA approved versions of any advertising materials for Yutrepia®.

Liquidia will produce documents responsive to UTC RFP No. 9 consistent with its objections and responses.

- **UTC RFP No. 11**

Regarding **UTC RFP No. 11**, UTC offers the same relevance theories that it used to argue the alleged relevance of UTC RFP Nos. 4-6 and 9. Liquidia finds any relevance theory that UTC proffered to justify RFP Nos. 4-6 and 9 above unconvincing, and it also finds any relevance theory (or lack thereof) unconvincing for RFP No. 11. It eludes Liquidia as to how financial *forecasts* for Yutrepia® could somehow be relevant to UTC's validity arguments as it suggests. To the extent UTC alludes to commercial success, *forecasts* are not actual sales, revenue or profit and is thus irrelevant to actual commercial success.

Regarding UTC's damages theories, Liquidia has already agreed to produce its actual financial information once Yutrepia® launches.

- **UTC RFP Nos. 12-14**

Regarding **UTC RFP Nos. 12-14**, as explained above, any plans or forecasts are irrelevant if Liquidia does not launch. Any plans or forecasts would become mooted once Liquidia does launch, as Liquidia will have produced its actual financial figures if and when Liquidia launches Yutrepia®.

In the spirit of compromise, Liquidia is willing to produce documents responsive to these request, if and when Liquidia launches, without limiting to a "sufficient to show" basis.

Regarding **UTC RFP No. 12**, Liquidia will produce documents relating to actual sales, sales quantities, units, gross sales, net sales, revenue, profits, variable and fixed costs, gross income, and net income for Yutrepia®. The only categories of documents that Liquidia is excluding are related to forecasted or potential information, which is not relevant to the claims and defenses in this litigation as UTC would not be entitled to damages based on this information, nor are they relevant to infringement or validity, as they do not reflect actual figures.

Regarding **RFP Nos. 13-14**, Liquidia will exclude documents related to forecasted or potential information, but will produce documents responsive to the remaining categories of information if and when Liquidia launches.

Liquidia has responded to each of UTC's relevance theories listed with respect to RFP No. 9 above and Liquidia does not see how UTC's requests are relevant now to the issues of infringement,



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validity, and willfulness. And Liquidia’s discovery obligations are not as broad and encompassing as UTC professes, as they are cabined by the Federal Rules of Civil Procedure.

- **UTC RFP No. 15**

Regarding **UTC RFP No. 15**, placement on a formulary is not relevant to infringement, damages, or validity, and UTC has provided no basis for the relevance of the documents that it seeks in this RFP. Liquidia has agreed to produce actual sales and other actual financial information if and when Liquidia launches. UTC argues that it is “entitled” to this information, but such information does not bear on the issues of infringement and objective indicia of non-obviousness, to which UTC has not identified which particular indicia is implicated. To the extent UTC argues that the information sought by this RFP is relevant to commercial success, we have agreed to produce actual sales and other actual financial information. Nevertheless, in the spirit of compromise, Liquidia is willing to produce actual formulary placement information if and when such formulary placement occurs.

- **UTC RFP No. 16**

In **UTC RFP No. 16**, UTC seeks documents “that reflect Liquidia’s **use** of any claim terms” It is unclear what the term “use” means and it is not explained in UTC’s RFPs nor in UTC’s Letter. To the extent that the term “use” refers to Liquidia’s usage of the claim terms in its own documents, UTC RFP No. 16 would require Liquidia to search *all* of its documents for usage of those terms, which is unquestionably unduly burdensome, irrelevant, and not proportional to the needs of the case. Furthermore, the RFP is not limited to the “use” of any claim terms in the context of PH-ILD to improve exercise capacity. Finally, Liquidia’s “use” of claim terms would not bear on claim construction, as they are, at most, extrinsic evidence with little to no probative value on claim construction. Liquidia’s “use” of claim terms would also not be relevant to issues of validity because such “use” would not be tied, in any way, to the asserted claims.

The parties have not yet conferred regarding UTC RFP No. 16, and Liquidia is willing to confer to determine the proper scope of this request.

- **UTC RFP No. 17 & Liquidia’s General Objection Relating to the “Relevant Time Period”**

Liquidia defined the “Relevant Time Period” to be from March 31, 2021 to September 5, 2023 because March 31, 2021 is the date on which Tyvaso was granted FDA approval to treat PH-ILD to improve exercise ability. The full six-year period contemplated by the Delaware Default Standard for Discovery would cover time periods before PH-ILD became relevant to Liquidia.

Regarding **UTC RFP No. 17**, Liquidia will produce responsive documents, including documents through the present day, on a rolling basis in a time frame commensurate with the scope of the Request.



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Liquidia is Amenable To The Provision of A Privilege Log From Both Parties

As UTC is aware, Liquidia has asserted inequitable conduct in this case. UTC's RFP and Interrogatory responses claim privilege, and thus assert that UTC will not produce or respond, to a host of relevant discovery requests on this basis. To the extent UTC intends to rely on privilege as a basis to withhold relevant information and documents related to at least inequitable conduct, a privilege log is required. Liquidia is willing to discuss privilege logs, and their scope, with UTC, but UTC has to be willing to produce such logs.

Liquidia Will Not Redact Subject Matter Based On Relevance

Regarding **UTC RFP Nos. 10 and 17**, Liquidia will not redact subject matter based on relevance. Liquidia's responses to both RFPs state that Liquidia will produce responsive documents on a rolling basis in a timeframe commensurate with the scope of the Request. Liquidia is not withholding documents and will produce documents responsive to UTC RFP Nos 10 and 17 in due course.

Sincerely,

Robert Minn

/s/ Robert Minn

cc: All counsel of record (via e-mail)

EXHIBIT 25

(12) **United States Patent**
Mosher et al.

(10) **Patent No.:** **US 10,786,482 B2**
(45) **Date of Patent:** ***Sep. 29, 2020**

(54) **ENALAPRIL FORMULATIONS**

(71) Applicant: **Silvergate Pharmaceuticals, Inc.**,
Greenwood Village, CO (US)

(72) Inventors: **Gerold L. Mosher**, Kansas City, MO
(US); **David W. Miles**, Kansas City,
MO (US)

(73) Assignee: **SILVERGATE**
PHARMACEUTICALS, INC.,
Greenwood Village, CO (US)

(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

This patent is subject to a terminal dis-
claimer.

(21) Appl. No.: **16/177,159**

(22) Filed: **Oct. 31, 2018**

(65) **Prior Publication Data**
US 2019/0070147 A1 Mar. 7, 2019

Related U.S. Application Data

(63) Continuation of application No. 16/003,994, filed on
Jun. 8, 2018, now Pat. No. 10,154,987, which is a
continuation of application No. 15/802,341, filed on
Nov. 2, 2017, now Pat. No. 10,039,745, which is a
continuation of application No. 15/613,622, filed on
(Continued)

(51) **Int. Cl.**
A61K 31/401 (2006.01)
A61K 9/00 (2006.01)
A61K 47/26 (2006.01)
A61K 47/12 (2006.01)

(52) **U.S. Cl.**

CPC **A61K 31/401** (2013.01); **A61K 9/0053**
(2013.01); **A61K 9/0095** (2013.01); **A61K**
47/12 (2013.01); **A61K 47/26** (2013.01)

(58) **Field of Classification Search**

CPC **A61K 31/401**; **A61K 47/12**; **A61K 47/26**;
A61K 9/0053; **A61K 9/0095**
See application file for complete search history.

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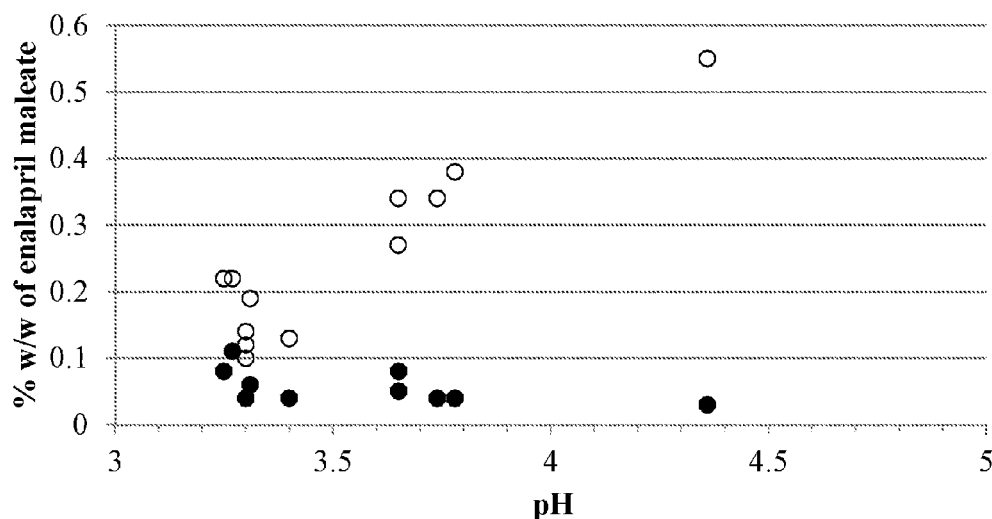
(74) *Attorney, Agent, or Firm* — Wilson, Sonsini,
Goodrich & Rosati, P.C.

(57) **ABSTRACT**

Provided herein are stable enalapril oral liquid formulations.
Also provided herein are methods of using enalapril oral
liquid formulations for the treatment of certain diseases
including hypertension, heart failure and asymptomatic left
ventricular dysfunction.

28 Claims, 2 Drawing Sheets

● Enalapril diketopiperazine; ○ Enalaprilat



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Related U.S. Application Data

Jun. 5, 2017, now Pat. No. 9,808,442, which is a continuation of application No. 15/081,603, filed on Mar. 25, 2016, now Pat. No. 9,669,008.

(60) Provisional application No. 62/310,198, filed on Mar. 18, 2016.

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U.S. Patent

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FIG. 1

● Enalapril diketopiperazine; ○ Enalaprilat

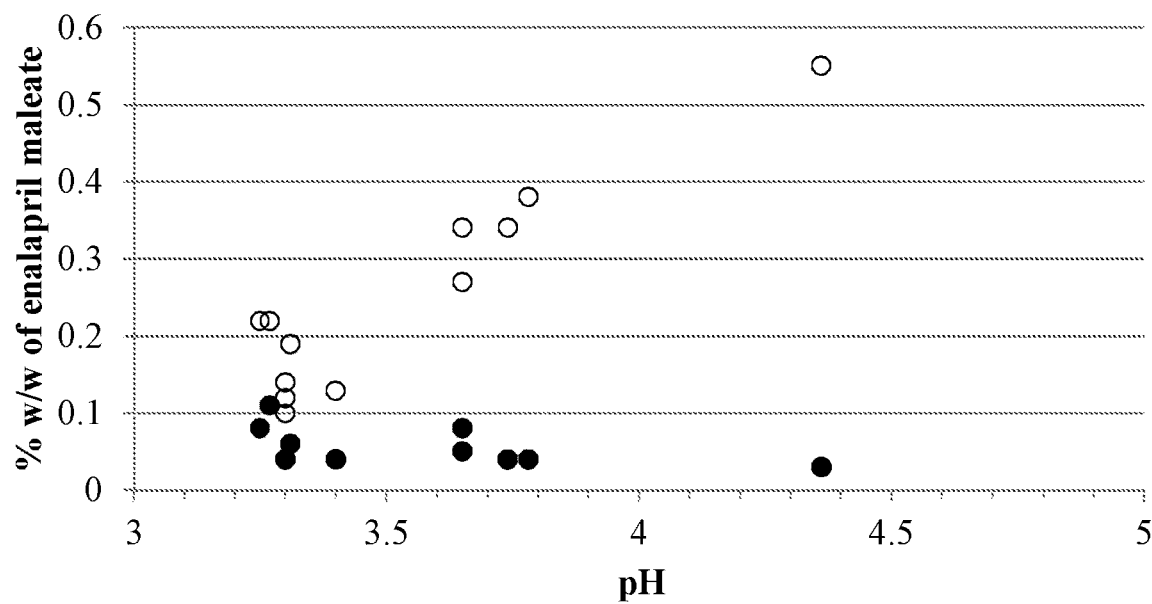
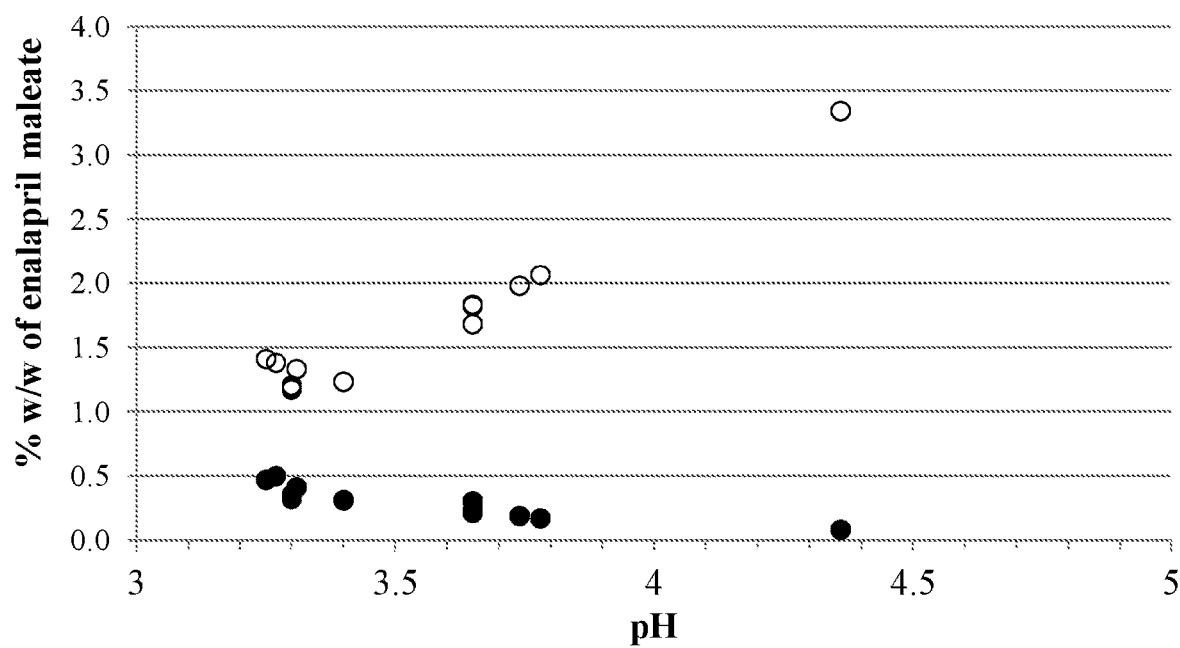


FIG. 2

● Enalapril diketopiperazine; ○ Enalaprilat



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ENALAPRIL FORMULATIONS

CROSS-REFERENCE OF RELATED APPLICATIONS

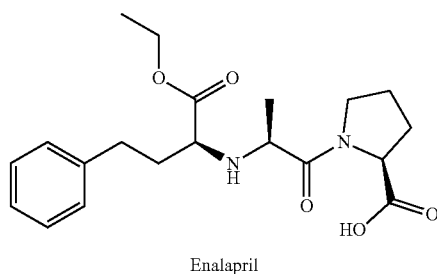
This application is a continuation of U.S. patent application Ser. No. 16/003,994, filed Jun. 8, 2018, which is a continuation of U.S. patent application Ser. No. 15/802,341, filed Nov. 2, 2017 (now U.S. Pat. No. 10,039,745, issued Aug. 7, 2018), which is a continuation of U.S. patent application Ser. No. 15/613,622, filed Jun. 5, 2017 (now U.S. Pat. No. 9,808,442, issued Nov. 7, 2017), which is a continuation of U.S. patent application Ser. No. 15/081,603, filed Mar. 25, 2016 (now U.S. Pat. No. 9,669,008, issued Jun. 6, 2017), which claims the benefit of U.S. Provisional Patent Application No. 62/310,198, filed Mar. 18, 2016, all of which are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

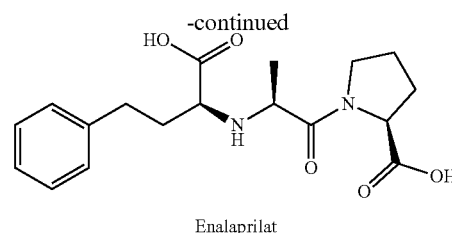
Hypertension, or high blood pressure, is a serious health issue in many countries. According to the National Heart Blood and Lung Institute, it is thought that about 1 in 3 adults in the United States alone have hypertension. Left unchecked, hypertension is considered a substantial risk factor for cardiovascular and other diseases including coronary heart disease, myocardial infarction, congestive heart failure, stroke and kidney failure. Hypertension is classified as primary (essential) hypertension or secondary hypertension. Primary hypertension has no known cause and may be related to a number of environmental, lifestyle and genetic factors such as stress, obesity, smoking, inactivity and sodium intake. Secondary hypertension can be caused by drug or surgical interventions, or by abnormalities in the renal, cardiovascular or endocrine system.

A number of antihypertensive drugs are available for treating hypertension. Various therapeutic classes of antihypertensive drugs include alpha-adrenergic blockers, beta-adrenergic blockers, calcium-channel blockers, hypotensives, mineralocorticoid antagonists, central alpha-agonists, diuretics and rennin-angiotensin-aldosterone inhibitors which include angiotensin II receptor antagonists (ARB) and angiotensin-converting enzyme (ACE) inhibitors. Angiotensin-converting enzyme (ACE) inhibitors inhibit angiotensin-converting enzyme (ACE), a peptidyl dipeptidase that catalyzes angiotension I to angiotension II, a potent vasoconstrictor involved in regulating blood pressure.

Enalapril is a prodrug belonging to the angiotensin-converting enzyme (ACE) inhibitor of medications. It is rapidly hydrolyzed in the liver to enalaprilat following oral administration. Enalaprilat acts as a potent inhibitor of ACE. The structural formulae of enalapril and enalaprilat are as follows:



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Enalapril is currently administered in the form of oral tablets, (e.g., Vasotec) or in the form of liquid formulations obtained by reconstitution of enalapril powder formulations. In addition to the treatment of hypertension, enalapril tablets have been used for symptomatic congestive heart failure, and asymptomatic left ventricular dysfunction.

SUMMARY OF THE INVENTION

Provided herein are enalapril oral liquid formulations. In one aspect, the enalapril oral liquid formulation, comprises (i) enalapril or a pharmaceutically acceptable salt or solvate thereof (ii) a sweetener that is sucralose (iii) a buffer comprising citric acid; (iv) a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5 \pm 3^\circ$ C. for at least 12 months.

In some embodiments, the enalapril is enalapril maleate. In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer in the formulation further comprises sodium citrate dihydrate. In some embodiments, the amount of enalapril or a pharmaceutically acceptable salt or solvate thereof is about 0.6 to about 1.2 mg/ml. In some embodiments, the amount of sucralose is about 0.5 to about 0.9 mg/ml. In some embodiments, the amount of citric acid in the buffer is about 0.8 to about 3.5 mg/ml. In some embodiments, the amount of sodium citrate dihydrate in the buffer is about 0.1 to about 0.80 mg/ml. In some embodiments, the amount of the sodium benzoate is about 0.2 to about 1.2 mg/ml. In some embodiments, the amount of enalapril or a pharmaceutically acceptable salt or solvate thereof is about 10 to about 25% (w/w of solids). In some embodiments, the amount of sucralose is about 8 to about 18% (w/w of solids). In some embodiments, the amount of citric acid in the buffer is about 17 to about 47% (w/w of solids). In some embodiments, the amount of sodium citrate dihydrate in the buffer is about 1 to about 11% (w/w of solids). In some embodiments, the amount of sodium benzoate is about 12 to about 25% (w/w of solids). In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about $5 \pm 3^\circ$ C. for at least 18 months. In some embodiments, the formulation is stable at about $5 \pm 3^\circ$ C. for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In one aspect, the enalapril oral liquid formulation, comprises (i) about 1 mg/ml enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water;

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wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months.

In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer further comprises about 0.15 mg/mL sodium citrate dihydrate. In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 18 months. In some embodiments, the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In one aspect, the enalapril oral liquid formulation comprises (i) about 19.3% (w/w of solids) enalapril maleate; (ii) about 13.5% (w/w of solids) of a sweetener that is sucralose; (iii) a buffer comprising about 35.2% (w/w of solids) citric acid; (iv) about 19.3% (w/w of solids) of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months.

In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer further comprises about 2.9% (w/w of solids) sodium citrate dihydrate. In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 18 months. In some embodiments, the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In one aspect, the enalapril oral liquid formulation consists essentially of (i) about 1 mg/mL enalapril maleate; (ii) about 0.70 mg/mL of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/mL citric acid and about 0.15 mg/mL sodium citrate dihydrate; (iv) about 1 mg/mL of a preservative that is sodium benzoate; (v) a flavoring agent; and (vi) water; wherein the pH of the formulation is less than about 3.5 adjusted by sodium hydroxide or hydrochloric acid; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months.

Also provided herein are methods of treating hypertension in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/mL enalapril maleate; (ii) about 0.7 mg/mL sucralose; (iii) a buffer comprising about 1.82 mg/mL citric acid and about 0.15 mg/mL sodium citrate dihydrate; (iv) about 1 mg/mL of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In some embodiments, the hypertension is primary (essential) hypertension. In some embodiments, the hypertension is secondary hypertension. In some embodiments, the subject has blood pressure values greater than or equal to 140/90 mm Hg. In some embodiments, the subject is an

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adult. In some embodiments, the subject is elderly. In some embodiments, the subject is a child. In some embodiments, the formulation is administered to the subject in a fasted state. In some embodiments, the formulation is administered to the subject in a fed state. In some embodiments, the formulation is further administered in combination with an agent selected from the group consisting of diuretics, beta blockers, alpha blockers, mixed alpha and beta blockers, calcium channel blockers, angiotensin II receptor antagonists, ACE inhibitors, aldosterone antagonists, and alpha-2 agonists.

Also provided herein are methods of treating prehypertension in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/mL enalapril maleate; (ii) about 0.7 mg/mL of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/mL citric acid and about 0.15 mg/mL sodium citrate dihydrate; (iv) about 1 mg/mL of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In some embodiments, the subject has blood pressure values of about 120-139/80-89 mm Hg.

Also provided herein are methods of treating heart failure in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/mL enalapril maleate; (ii) about 0.70 mg/mL of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/mL citric acid and about 0.15 mg/mL sodium citrate dihydrate; (iv) about 1 mg/mL of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

Also provided herein are methods of treating left ventricular dysfunction in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/mL enalapril maleate; (ii) about 0.7 mg/mL of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/mL citric acid and about 0.15 mg/mL sodium citrate dihydrate; (iv) about 1 mg/mL of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

INCORPORATION BY REFERENCE

All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed descrip-

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tion that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

FIG. 1: Effect of pH on degradant formation after 8 weeks of storage of various enalapril solution formulations at 5° C.

FIG. 2: Effect of pH on degradant formation after 8 weeks of storage of various enalapril solution formulations at room temperature (19-22° C.).

DETAILED DESCRIPTION OF THE INVENTION

Provided herein are stable enalapril oral liquid formulations. Also provided herein are stable enalapril powder formulations for reconstitution for oral liquid administration. These enalapril formulations described herein are useful for the treatment of hypertension, prehypertension, heart failure as well as ventricular dysfunction. The formulations are advantageous over conventional solid dosage administration of enalapril ranging from ease of administration, accuracy of dosing, accessibility to additional patient populations such as to children and the elderly, and an increased patient compliance to medication.

It is generally known that certain segments of the population have difficulty ingesting and swallowing solid oral dosage forms such as tablets and capsules. As many as a quarter of the total population has this difficulty. Often, this leads to non-compliance with the recommended medical therapy with the solid dosage forms, thereby resulting in rendering the therapy ineffective. Further, solid dosage forms are not recommended for children or elderly due to increased risk in choking.

Furthermore, the dose of enalapril to be given to children is calculated according to the child's weight. When the calculated dose is something other than the amount present in one or more intact solid dosage forms, the solid dosage form must be divided to provide the correct dose. This leads to inaccurate dosing when solid dosages forms, such as tablets, are compounded to prepare other formulations for children.

For enalapril, one solution to overcoming the use of the tablet form is for a compounding pharmacist to pulverize and crush the enalapril tablet(s) into a powder via mortar and pestle and reconstitute the powder in some liquid form. However forming a enalapril oral liquid in this fashion has significant drawbacks including large variability in the actual dosage, incomplete solubilizing of the enalapril tablet in the liquid, rapid instability, inconsistent formulation methods per compounding pharmacy, and a number of other potential issues. The crushed tablet liquid formulation may also be potentially unsafe due to contamination with residual drugs and other substances from the mortar and pestle or other crushing agent.

Alternatively, enalapril is formulated as enalapril powder compositions for reconstitution as oral liquids as described in U.S. Pat. No. 8,568,747. The powder compositions as described in this patent require mannitol and colloidal silicon dioxide for stability and dissolution. While these powder compositions are an improvement over crushing tablets, they still require a step of mixing with a diluent. The stable enalapril oral liquid formulations described herein require no extra steps or manipulation prior to administration to a subject. Further, the stable enalapril oral liquid formulations described herein do not require or need mannitol or colloidal silicon dioxide for stability and dissolution.

The present embodiments described herein provide a safe and effective oral administration of enalapril for the treat-

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ment of hypertension and other disorders. In particular, the embodiments provide stable enalapril oral liquid formulations as well as alternatively enalapril powder formulations for oral liquid administration.

As used herein, "enalapril" refers to enalapril base, its salt, or solvate or derivative or isomer or polymorph thereof. Suitable compounds include the free base, the organic and inorganic salts, isomers, isomer salts, solvates, polymorphs, complexes etc. U.S. Pat. Nos. 4,374,829; 4,472,380 and 4,510,083 disclose exemplary methods in the preparation of enalapril. In some embodiments, the enalapril used in the formulations described herein is an enalapril salt. In some instances, the enalapril salt is enalapril maleate. In other instances, the enalapril salt is in the form of enalapril sodium.

Other ACE inhibitors are contemplated in the formulations within and include but are not limited to quinapril, indolapril, ramipril, perindopril, lisinopril, benazepril, imidapril, zofenopril, trandolapril, fosinopril, captopril, and their salts, solvates, derivatives, polymorphs, or complexes, thereof.

Enalapril Oral Liquid Formulations

Oral liquids include, but are not limited to, solutions (both aqueous and nonaqueous), suspensions, emulsions, syrups, slurries, juices, elixirs, dispersions, and the like. It is envisioned that solution/suspensions are also included where certain components described herein are in a solution while other components are in a suspension.

In one aspect, the enalapril liquid formulations described herein comprise enalapril, a preservative, a sweetening agent, a buffer, and water. In one embodiment, the sweetening agent is sucralose. In one embodiment, the sweetening agent is xylitol. In one embodiment, the sweetening agent is not mannitol. In another embodiment, the preservative is sodium benzoate. In some embodiments, the preservative is a paraben. In some embodiments, the preservative is a mixture of parabens. In yet another embodiment, the buffer comprises citric acid. In some embodiments, the buffer further comprises sodium citrate. In one aspect, the enalapril liquid formulation described herein comprises enalapril, sucralose, sodium benzoate, citric acid, sodium citrate, and water. In some embodiments, the enalapril liquid formulation herein further comprises a flavoring agent. In some embodiments, the enalapril liquid formulation is not obtained from crushing enalapril tablet and dissolving the powder in a suitable vehicle for oral administration. In some embodiments, the enalapril liquid formulation does not contain silicon dioxide. In some embodiments, the enalapril liquid formulation does not contain mannitol. In some embodiments, the enalapril liquid formulation does not contain lactose. In some embodiments, the enalapril liquid formulation does not contain magnesium stearate. In some embodiments, the enalapril liquid formulation does not contain sodium bicarbonate. In some embodiments, the enalapril liquid formulation does not contain iron oxides.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.6 to about 1.2 mg/ml in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83

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mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/ml, about 0.91 mg/ml, about 0.92 mg/ml, about 0.93 mg/ml, about 0.94 mg/ml, about 0.95 mg/ml, about 0.96 mg/ml, about 0.97 mg/ml, about 0.98 mg/ml, about 0.99 mg/ml, about 1 mg/ml, about 1.01 mg/ml, about 1.02 mg/ml, about 1.03 mg/ml, about 1.04 mg/ml, about 1.05 mg/ml, about 1.06 mg/ml, about 1.07 mg/ml, about 1.08 mg/ml, about 1.09 mg/ml, about 1.1 mg/ml, about 1.11 mg/ml, about 1.12 mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, or about 1.2 mg/ml in the liquid oral formulation. In some embodiments, enalapril is present in about 0.76 mg/ml in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 1 mg/ml in the oral liquid formulation. In some embodiments, the formulation contains enalapril or another pharmaceutically acceptable salt of enalapril in a molar concentration equivalent to 1 mg/mL enalapril maleate. In some embodiments, the formulation contains enalapril or another pharmaceutically acceptable salt of enalapril in a molar concentration equivalent to 0.76 mg/mL enalapril.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w to about 30% w/w of the solids in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w, about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about 15.1% w/w, about 15.2% w/w, about 15.3% w/w, about 15.4% w/w, about 15.5% w/w, about 15.6% w/w, about 15.7% w/w, about 15.8% w/w, about 15.9% w/w, about 16% w/w, about 16.1% w/w, about 16.2% w/w, about 16.3% w/w, about 16.4% w/w, about 16.5% w/w, about 16.6% w/w, about 16.7% w/w, about 16.8% w/w, about 16.9% w/w, about 17% w/w, about 17.1% w/w, about 17.2% w/w, about 17.3% w/w, about 17.4% w/w, about 17.5% w/w, about 17.6% w/w, about 17.7% w/w, about 17.8% w/w, about 17.9% w/w, about 18% w/w, about 18.1% w/w, about 18.2% w/w, about 18.3% w/w, about 18.4% w/w, about 18.5% w/w, about 18.6% w/w, about 18.7% w/w, about 18.8% w/w, about 18.9% w/w, about 19% w/w, about 19.1% w/w, about 19.2% w/w, about 19.3% w/w, about 19.4% w/w, about 19.5% w/w, about 19.6% w/w, about 19.7% w/w, about 19.8% w/w, about 19.9% w/w, about 20% w/w, about 20.1% w/w, about 20.2% w/w, about 20.3% w/w, about 20.4% w/w, about 20.5% w/w, about 20.6% w/w, about 20.7% w/w, about 20.8% w/w, about 20.9% w/w, about 21% w/w, about 21.1% w/w, about 21.2% w/w, about 21.3% w/w, about 21.4% w/w, about 21.5% w/w, about 21.6% w/w, about 21.7% w/w, about 21.8% w/w, about 21.9% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5% w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 10% w/w to about 25% w/w of the solids in the oral liquid formulation. In some embodi-

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ments, enalapril is present in about 10.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 15% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 18.2% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 13.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 19.3% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 24.5% w/w of the solids in the oral liquid formulation.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w to about 1% w/w of the solids in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w, about 0.15% w/w, about 0.2% w/w, about 0.25% w/w, about 0.3% w/w, about 0.35% w/w, about 0.4% w/w, about 0.45% w/w, about 0.5% w/w, about 0.55% w/w, about 0.6% w/w, about 0.65% w/w, about 0.7% w/w, about 0.75% w/w, about 0.8% w/w, about 0.85% w/w, about 0.9% w/w, about 0.95% w/w, or about 1% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.4% w/w to about 0.7% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 0.4% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 0.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 0.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 0.6% w/w of the solids in the oral liquid formulation.

Sweetener in the Enalapril Oral Liquid Formulations

Sweeteners or sweetening agents include any compounds that provide a sweet taste. This includes natural and synthetic sugars, natural and artificial sweeteners, natural extracts and any material that initiates a sweet sensation in a subject. In some embodiments, a solid/powder sweetener is used in the oral liquid formulation described herein. In other embodiments, a liquid sweetener is used in the oral liquid formulation described herein.

Sugars illustratively include glucose, fructose, sucrose, xylitol, tagatose, sucralose, maltitol, isomaltulose, Isomalt™ (hydrogenated isomaltulose), lactitol, sorbitol, erythritol, trehalose, maltodextrin, polydextrose, and the like. Other sweeteners illustratively include glycerin, inulin, erythritol, maltol, acesulfame and salts thereof, e.g., acesulfame potassium, alitame, aspartame, neotame, sodium cyclamate, saccharin and salts thereof, e.g., saccharin sodium or saccharin calcium, neohesperidin dihydrochalcone, stevioside, thaumatin, and the like. Sweeteners can be used in the form of crude or refined products such as hydrogenated starch hydrolysates, maltitol syrup, high fructose corn syrup, etc., and as branded products, e.g., Sweet Am™ liquid (Product Code 918.003-propylene glycol, ethyl alcohol, and proprietary artificial flavor combination, Flavors of North America) and Sweet Am™ powder (Product Code 918.005-maltodextrin, sorbitol, and fructose combination and Product Code 918.010-water, propylene glycol, sorbitol, fructose, and proprietary natural and artificial flavor combination, Flavors of North America), ProSweet™ (1-10% proprietary plant/vegetable extract and 90-99% dextrose combination, Virginia Dare), Maltisweet™ (maltitol solution, Ingredient), Sorbo™ (sorbitol and sorbitol/xylitol solution, SPI Polyols), Invertose™ (high fructose corn

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syrup, Ingredient), Rebalance M60 and X60 (sucralose and maltodextrin, Tate and Lyle), and Ora-Sweet® sugar-free flavored syrup (Paddock Laboratories, Inc.). Sweeteners can be used singly or in combinations of two or more. Suitable concentrations of different sweeteners can be selected based on published information, manufacturers' data sheets and by routine testing.

In some embodiments, the enalapril oral liquid formulation described herein comprises a sweetening agent. In some embodiments, the sweetening agent is sucralose. In some embodiments, the sweetening agent is xylitol. In some embodiments, the sweetener is not mannitol.

In some embodiments, the enalapril oral liquid formulation described herein comprises sucralose. In some embodiments, sucralose is present in about 0.5 to about 0.9 mg/ml in the oral liquid formulation. In other embodiments, sucralose is present in about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml, about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.60 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.70 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.80 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, or about 0.90 mg/ml in the oral liquid formulation. In some embodiments, sucralose is present in about 0.7 mg/ml in the oral liquid formulation.

In some embodiments, sucralose is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about 15.5% w/w, about 16% w/w, about 16.5% w/w, about 17% w/w, about 17.5% w/w, about 18% w/w, about 18.5% w/w, about 19% w/w, about 19.5% w/w, about 20% w/w, about 20.5% w/w, about 21% w/w, about 21.5% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5% w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 8% w/w to about 18% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 9.5% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 13.5% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 16.5% w/w of the solids in the oral liquid formulation.

In some embodiments, the enalapril oral liquid formulation described herein comprises xylitol. In some embodiments, xylitol is present in about 140 mg/ml to about 210 mg/ml in the oral liquid formulation.

In some embodiments, xylitol is present in about 140 mg/ml, about 145 mg/ml, about 150 mg/ml, about 155

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mg/ml, about 160 mg/ml, about 165 mg/ml, about 170 mg/ml, about 175 mg/ml, about 180 mg/ml, about 185 mg/ml, about 190 mg/ml, about 195 mg/ml, about 200 mg/ml, about 205 mg/ml, or about 210 mg/ml of the oral liquid formulation. In some embodiments, xylitol is present in about 150 mg/ml in the oral liquid formulation. In some embodiments, xylitol is present in about 200 mg/ml in the oral liquid formulation.

In some embodiments, xylitol is present in about 80% w/w to about 99% w/w of the solids in the oral liquid formulation. In other embodiments, xylitol is present in about 80% w/w, about 81% w/w, about 82% w/w, about 83% w/w, about 84% w/w, about 85% w/w, about 86% w/w, about 87% w/w, about 88% w/w, about 89% w/w, about 90% w/w, about 91% w/w, about 92% w/w, about 93% w/w, about 94% w/w, about 95% w/w, about 96% w/w, about 97% w/w, about 98% w/w, or about 99% w/w of the solids in the oral liquid formulation. In some embodiments, xylitol is present in about 96% w/w to about 98% w/w of the solids in the oral liquid formulation. In some embodiments, xylitol is present in about 96% w/w of the solids in the oral liquid formulation.

Preservative in the Enalapril Oral Liquid Formulations

Preservatives include anti-microbials, anti-oxidants, and agents that enhance sterility. Exemplary preservatives include ascorbic acid, ascorbyl palmitate, BHA, BHT, citric acid, EDTA and its salts, erythorbic acid, fumaric acid, malic acid, propyl gallate, sodium ascorbate, sodium bisulfate, sodium metabisulfite, sodium sulfite, parabens (such as methylparaben, ethylparaben, propylparaben, butylparaben and their salts), benzoic acid, sodium benzoate, potassium sorbate, vanillin, and the like.

In some embodiments, the enalapril oral liquid formulation described herein comprises a preservative.

In some embodiments, the preservative is a paraben and the sweetener is not a sugar (such as, but not limited to glucose, fructose, sucrose, lactose, maltose) or a sugar alcohol (such as, but not limited to xylitol, mannitol, lactitol, maltitol, sorbitol).

In some embodiments, the preservative is sodium benzoate.

In some embodiments, modulation of the pH is desired to provide the best antimicrobial activity of the preservative, sodium benzoate. In some embodiments, the antimicrobial activity of sodium benzoate drops when the pH is increased above 5.

In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, or about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3.3.

In some embodiments, sodium benzoate is present in about 0.2 to about 1.2 mg/ml in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 0.2 mg/ml, about 0.21 mg/ml, about 0.22 mg/ml, about 0.23 mg/ml, about 0.24 mg/ml, about 0.25 mg/ml, about 0.26 mg/ml, about 0.27 mg/ml, about 0.28 mg/ml, about 0.29 mg/ml, about 0.3 mg/ml, about 0.31 mg/ml, about 0.32

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mg/ml, about 0.33 mg/ml, about 0.34 mg/ml, about 0.35 mg/ml, about 0.36 mg/ml, about 0.37 mg/ml, about 0.38 mg/ml, about 0.39 mg/ml, about 0.4 mg/ml, about 0.41 mg/ml, about 0.42 mg/ml, about 0.43 mg/ml, about 0.44 mg/ml, about 0.45 mg/ml, about 0.46 mg/ml, about 0.47 mg/ml, about 0.48 mg/ml, about 0.49 mg/ml, about 0.5 mg/ml, about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml, about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/ml, about 0.91 mg/ml, about 0.92 mg/ml, about 0.93 mg/ml, about 0.94 mg/ml, about 0.95 mg/ml, about 0.96 mg/ml, about 0.97 mg/ml, about 0.98 mg/ml, about 0.99 mg/ml, about 1 mg/ml, about 1.01 mg/ml, about 1.02 mg/ml, about 1.03 mg/ml, about 1.04 mg/ml, about 1.05 mg/ml, about 1.06 mg/ml, about 1.07 mg/ml, about 1.08 mg/ml, about 1.09 mg/ml, about 1.1 mg/ml, about 1.11 mg/ml, about 1.12 mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, or about 1.2 mg/ml in the liquid oral formulation. In some embodiments, sodium benzoate is present in about 1 mg/ml in the oral liquid formulation.

In some embodiments, sodium benzoate is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about 15.1% w/w, about 15.2% w/w, about 15.3% w/w, about 15.4% w/w, about 15.5% w/w, about 15.6% w/w, about 15.7% w/w, about 15.8% w/w, about 15.9% w/w, about 16% w/w, about 16.1% w/w, about 16.2% w/w, about 16.3% w/w, about 16.4% w/w, about 16.5% w/w, about 16.6% w/w, about 16.7% w/w, about 16.8% w/w, about 16.9% w/w, about 17% w/w, about 17.1% w/w, about 17.2% w/w, about 17.3% w/w, about 17.4% w/w, about 17.5% w/w, about 17.6% w/w, about 17.7% w/w, about 17.8% w/w, about 17.9% w/w, about 18% w/w, about 18.1% w/w, about 18.2% w/w, about 18.3% w/w, about 18.4% w/w, about 18.5% w/w, about 18.6% w/w, about 18.7% w/w, about 18.8% w/w, about 18.9% w/w, about 19% w/w, about 19.1% w/w, about 19.2% w/w, about 19.3% w/w, about 19.4% w/w, about 19.5% w/w, about 19.6% w/w, about 19.7% w/w, about 19.8% w/w, about 19.9% w/w, about 20% w/w, about 20.1% w/w, about 20.2% w/w, about 20.3% w/w, about 20.4% w/w, about 20.5% w/w, about 20.6% w/w, about 20.7% w/w, about 20.8% w/w, about 20.9% w/w, about 21% w/w, about 21.1% w/w, about 21.2% w/w, about 21.3% w/w, about 21.4% w/w, about 21.5% w/w, about 21.6% w/w, about 21.7% w/w, about 21.8% w/w, about 21.9% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5%

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w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 10% w/w to about 25% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 13.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 19.3% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 23.5% w/w of the solids in the oral liquid formulation.

In some embodiments, sodium benzoate is present in about 0.1% w/w to about 1% w/w of the solids in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 0.1% w/w, about 0.15% w/w, about 0.2% w/w, about 0.25% w/w, about 0.3% w/w, about 0.35% w/w, about 0.4% w/w, about 0.45% w/w, about 0.5% w/w, about 0.55% w/w, about 0.6% w/w, about 0.65% w/w, about 0.7% w/w, about 0.75% w/w, about 0.8% w/w, about 0.85% w/w, about 0.9% w/w, about 0.95% w/w, or about 1% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.4% w/w to about 0.7% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.45% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.6% w/w of the solids in the oral liquid formulation.

In some embodiments, sodium benzoate is present in an amount sufficient to provide antimicrobial effectiveness to the enalapril oral liquid formulation described herein. (See Table G-1).

In some embodiments, the preservative is a paraben. In some embodiments, the preservative is a mixture of parabens. In some embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml to about 2 mg/ml in the oral liquid formulation. In other embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml, about 0.2 mg/ml, about 0.3 mg/ml, about 0.4 mg/ml, about 0.5 mg/ml, about 0.6 mg/ml, about 0.7 mg/ml, about 0.8 mg/ml, about 0.9 mg/ml, about 1 mg/ml, about 1.1 mg/ml, about 1.2 mg/ml, about 1.3 mg/ml, about 1.4 mg/ml, or about 1.5 mg/ml, about 1.6 mg/ml, about 1.7 mg/ml, about 1.8 mg/ml, about 1.9 mg/ml, or about 2 mg/ml in the liquid oral formulation. In some embodiments, the paraben or mixture of parabens is present in about 1.6 mg/ml to about 2 mg/ml in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 1.6 mg/ml to about 1.8 mg/ml in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml to about 0.5 mg/ml in the oral liquid formulation.

In some embodiments, the paraben or mixture of parabens is present in about 2% w/w to about 30% w/w of the solids in the oral liquid formulation. In other embodiments, the paraben or mixture of parabens is present in about 2% w/w, about 3% w/w, about 4% w/w, about 5% w/w, about 6% w/w, about 7% w/w, about 8% w/w, about 9% w/w, about 10% w/w, about 11% w/w, about 12% w/w, about 13% w/w, about 14% w/w, about 15% w/w, about 16% w/w, about 17% w/w, about 18% w/w, about 19% w/w, about 20% w/w, about 21% w/w, about 22% w/w, about 23% w/w, about 24% w/w, about 25% w/w, about 26% w/w, about 27% w/w, about 28% w/w, about 29% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 2%

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w/w to about 3% w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 23% w/w to about 26% w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 26% w/w to about 30% w/w of the solids in the oral liquid formulation.

Sweetener and Preservative Incompatibility

Paraben preservatives (especially methylparaben) can react with selected sugars (glucose, fructose, sucrose, lactose, maltose) and sugar alcohols (xylitol, mannitol, lactitol, maltitol, sorbitol) to form transesterification reaction products. This can be undesirable from a formulation and stability standpoint as the transesterification creates additional degradants.

In some embodiments, the enalapril oral liquid formulation described herein does not comprise a paraben preservative. In further embodiments, the enalapril oral liquid formulation described herein does not comprise a paraben preservative when the formulation also comprises a sugar or sugar alcohol.

pH of Enalapril Oral Liquid Formulations

Buffering agents maintain the pH of the liquid enalapril formulation. Non-limiting examples of buffering agents include, but are not limited to sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium glucomate, aluminum hydroxide, aluminum hydroxide/sodium bicarbonate co-precipitate, mixture of an amino acid and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer. Additional buffering agents include citric acid, sodium citrate, sodium tartarate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, sodium acetate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, and other calcium salts. Some buffering agents also impart effervescent qualities when a powder is reconstituted in a solution. In some embodiments, the buffering agent is not sodium bicarbonate.

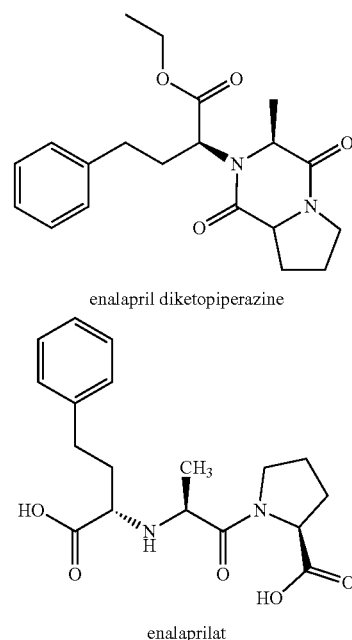
In some embodiments, the oral liquid formulation comprises a buffer.

In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid and sodium citrate. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid and sodium citrate dihydrate or an equivalent molar amount of sodium citrate anhydrous. In some embodiments, the sodium citrate is monosodium citrate. In some embodiments, the sodium citrate is disodium citrate. In some embodiments, the sodium citrate is trisodium citrate.

In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises phosphoric acid. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises sodium phosphate.

In some embodiments, modulation of the pH is desired to provide a lowered impurity profile. In the exemplary stability studies, the main enalapril degradants are enalapril diketopiperazine and enalaprilat:

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In some embodiments, the percentage of enalaprilat formation is increased when the pH is above 3.5. (See table C-2 and FIG. 1 and FIG. 2). In some embodiments, the percentage of enalapril diketopiperazine formation is slightly increased as the pH is below 4.

In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, or about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3.3.

In some embodiments, the formation of degradants is dependent on the buffer concentration. In some embodiments, the buffer concentration impacts the taste of the enalapril oral liquid formulation.

In some embodiments, the buffer concentration is between about 5 mM and about 20 mM. In some embodiments, the buffer concentration is about 5 mM, about 6 mM, about 7 mM, about 8 mM, about 9 mM, about 10 mM, about 11 mM, about 12 mM, about 13 mM, about 14 mM, about 15 mM, about 16 mM, about 17 mM, about 18 mM, about 19 mM, or about 20 mM. In some embodiments, the buffer concentration is about 5 mM. In some embodiments, the buffer concentration is about 10 mM. In some embodiments, the buffer concentration is about 20 mM.

In some embodiments, citric acid is present in about 0.7 to about 2 mg/ml in the oral liquid formulation. In other embodiments, citric acid is present in about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml,

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about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/mL, about 0.91 mg/mL, about 0.92 mg/mL, about 0.93 mg/mL, about 0.94 mg/mL, about 0.95 mg/mL, about 0.96 mg/mL, about 0.97 mg/mL, about 0.98 mg/mL, about 0.99 mg/mL, about 1 mg/mL, about 1.11 mg/ml, about 1.12 mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, about 1.2 mg/ml, about 1.21 mg/ml, about 1.22 mg/ml, about 1.23 mg/ml, about 1.24 mg/ml, about 1.25 mg/ml, about 1.26 mg/ml, about 1.27 mg/ml, about 1.28 mg/ml, about 1.29 mg/ml, about 1.3 mg/mL, about 1.31 mg/mL, about 1.32 mg/mL, about 1.33 mg/mL, about 1.34 mg/mL, about 1.35 mg/mL, about 1.36 mg/mL, about 1.37 mg/mL, about 1.38 mg/mL, about 1.39 mg/mL, about 1.4 mg/ml, about 1.41 mg/ml, about 1.42 mg/ml, about 1.43 mg/ml, about 1.44 mg/ml, about 1.45 mg/ml, about 1.46 mg/ml, about 1.47 mg/ml, about 1.48 mg/ml, about 1.49 mg/ml, about 1.5 mg/ml, about 1.51 mg/ml, about 1.52 mg/ml, about 1.53 mg/ml, about 1.54 mg/ml, about 1.55 mg/ml, about 1.56 mg/ml, about 1.57 mg/ml, about 1.58 mg/ml, about 1.59 mg/ml, about 1.6 mg/mL, about 1.61 mg/mL, about 1.62 mg/mL, about 1.63 mg/mL, about 1.64 mg/mL, about 1.65 mg/mL, about 1.66 mg/mL, about 1.67 mg/mL, about 1.68 mg/mL, about 1.69 mg/mL, about 1.7 mg/ml, about 1.71 mg/ml, about 1.72 mg/ml, about 1.73 mg/ml, about 1.74 mg/ml, about 1.75 mg/ml, about 1.76 mg/ml, about 1.77 mg/ml, about 1.78 mg/ml, about 1.79 mg/ml, about 1.8 mg/ml, about 1.81 mg/ml, about 1.82 mg/ml, about 1.83 mg/ml, about 1.84 mg/ml, about 1.85 mg/ml, about 1.86 mg/ml, about 1.87 mg/ml, about 1.88 mg/ml, about 1.89 mg/ml, about 1.9 mg/mL, about 1.91 mg/mL, about 1.92 mg/mL, about 1.93 mg/mL, about 1.94 mg/mL, about 1.95 mg/mL, about 1.96 mg/mL, about 1.97 mg/mL, about 1.98 mg/mL, about 1.99 mg/mL, or about 2 mg/mL in the oral liquid formulation. In some embodiments, citric acid is present in about 1.65 mg/ml in the oral liquid formulation. In some embodiments, citric acid is present in about 1.82 mg/ml in the oral liquid formulation. In some embodiments, citric acid is present in about 0.82 mg/ml in the oral liquid formulation.

In some embodiments, citric acid is present in about 2 to about 3.5 mg/ml in the oral liquid formulation. In other embodiments, citric acid is present in about 2 mg/mL, about 2.05 mg/mL, about 2.1 mg/mL, about 2.15 mg/mL, about 2.2 mg/mL, about 2.25 mg/mL, about 2.3 mg/mL, about 2.35 mg/mL, about 2.4 mg/mL, about 2.45 mg/mL, about 2.5 mg/mL, about 2.55 mg/mL, about 2.6 mg/mL, about 2.65 mg/mL, about 2.7 mg/mL, about 2.75 mg/mL, about 2.8 mg/mL, about 2.85 mg/mL, about 2.9 mg/mL, about 2.95 mg/mL, about 3 mg/mL, about 3.05 mg/ml, about 3.1 mg/mL, about 3.15 mg/mL, about 3.2 mg/mL, about 3.25 mg/mL, about 3.3 mg/mL, about 3.35 mg/mL, about 3.4 mg/mL, about 3.45 mg/mL, or about 3.5 mg/mL in the oral liquid formulation. In some embodiments, citric acid is present in about 3.3 mg/ml in the oral liquid formulation.

In some embodiments, citric acid is present in about 10% w/w to about 50% w/w of the solids in the oral liquid formulation. In other embodiments, citric acid is present in about 10% w/w, about 11% w/w, about 12% w/w, about 13% w/w, about 14% w/w, about 15% w/w, about 16% w/w, about 17% w/w, about 18% w/w, about 19% w/w, about 20% w/w, about 21% w/w, about 22% w/w, about 23% w/w, about 24% w/w, about 25% w/w, about 26% w/w, about 27% w/w, about 28% w/w, about 29% w/w, about 30% w/w, about 31% w/w, about 32% w/w, about 33% w/w, about 34%

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w/w, about 35% w/w, about 36% w/w, about 37% w/w, about 38% w/w, about 39% w/w, about 40% w/w, about 41% w/w, about 42% w/w, about 43% w/w, about 44% w/w, about 45% w/w, about 46% w/w, about 47% w/w, about 48% w/w, about 49% w/w, about 50% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 45% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 31% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 35% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 19% w/w of the solids in the oral liquid formulation.

In some embodiments, citric acid is present in about 1% w/w to about 5% w/w of the solids in the oral liquid formulation. In other embodiments, citric acid is present in about 1% w/w, about 1.1% w/w, about 1.2% w/w, about 1.3% w/w, about 1.4% w/w, about 1.5% w/w, about 1.6% w/w, about 1.7% w/w, about 1.8% w/w, about 1.9% w/w, about 2% w/w, about 2.1% w/w, about 2.2% w/w, about 2.3% w/w, about 2.4% w/w, about 2.5% w/w, about 2.6% w/w, about 2.7% w/w, about 2.8% w/w, about 2.9% w/w, about 3% w/w, about 3.1% w/w, about 3.2% w/w, about 3.3% w/w, about 3.4% w/w, about 3.5% w/w, about 3.6% w/w, about 3.7% w/w, about 3.8% w/w, about 3.9% w/w, about 4% w/w, about 4.1% w/w, about 4.2% w/w, about 4.3% w/w, about 4.4% w/w, about 4.5% w/w, about 4.6% w/w, about 4.7% w/w, about 4.8% w/w, about 4.9% w/w, or about 5% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 2.1% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 1.6% w/w of the solids in the oral liquid formulation.

In some embodiments, sodium citrate dihydrate is present in about 0.1 to about 0.8 mg/ml in the oral liquid formulation. In other embodiments, sodium citrate dihydrate is present in the oral liquid formulation is about 0.1 mg/mL, about 0.11 mg/mL, about 0.12 mg/mL, about 0.13 mg/mL, about 0.14 mg/mL, about 0.15 mg/mL, about 0.16 mg/mL, about 0.17 mg/mL, about 0.18 mg/mL, about 0.19 mg/mL, about 0.2 mg/ml, about 0.21 mg/ml, about 0.22 mg/ml, about 0.23 mg/ml, about 0.24 mg/ml, about 0.25 mg/ml, about 0.26 mg/ml, about 0.27 mg/ml, about 0.28 mg/ml, about 0.29 mg/ml, about 0.3 mg/ml, about 0.31 mg/ml, about 0.32 mg/ml, about 0.33 mg/ml, about 0.34 mg/ml, about 0.35 mg/ml, about 0.36 mg/ml, about 0.37 mg/ml, about 0.38 mg/ml, about 0.39 mg/ml, about 0.4 mg/ml, about 0.41 mg/ml, about 0.42 mg/ml, about 0.43 mg/ml, about 0.44 mg/ml, about 0.45 mg/ml, about 0.46 mg/ml, about 0.47 mg/ml, about 0.48 mg/ml, about 0.49 mg/ml, about 0.5 mg/ml, about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml, about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, or about 0.8 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.75 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.35 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.2 mg/ml in the

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oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.15 mg/ml in the oral liquid formulation.

In some embodiments, sodium citrate dihydrate is present in about 1% w/w to about 15% w/w of the solids in the oral liquid formulation. In other embodiments, sodium citrate dihydrate is present in about 1% w/w, about 1.1% w/w, about 1.2% w/w, about 1.3% w/w, about 1.4% w/w, about 1.5% w/w, about 1.6% w/w, about 1.7% w/w, about 1.8% w/w, about 1.9% w/w, about 2% w/w, about 2.1% w/w, about 2.2% w/w, about 2.3% w/w, about 2.4% w/w, about 2.5% w/w, about 2.6% w/w, about 2.7% w/w, about 2.8% w/w, about 2.9% w/w, about 3% w/w, about 3.1% w/w, about 3.2% w/w, about 3.3% w/w, about 3.4% w/w, about 3.5% w/w, about 3.6% w/w, about 3.7% w/w, about 3.8% w/w, about 3.9% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 10.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 7.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 4.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 2.9% w/w of the solids in the oral liquid formulation.

In other embodiments, sodium citrate dihydrate is not added to the formulation.

Additional Excipients

In further embodiments, the enalapril liquid formulation described herein comprises additional excipients including, but not limited to, glidants, flavoring agents, coloring agents and thickeners. Additional excipients such as bulking agents, tonicity agents and chelating agents are within the scope of the embodiments.

Glidants are substances that improve flowability of a powder. Suitable glidants include, but are not limited to, calcium phosphate tribasic, calcium silicate, cellulose (powdered), colloidal silicon dioxide, magnesium silicate, magnesium trisilicate, silicon dioxide, starch, talc and the like. In some embodiments, the enalapril powder formulations described herein comprise a glidant. In some embodiments the glidant is not colloidal silicon dioxide.

In another embodiment, the enalapril liquid formulation comprises a flavoring agent or flavorant to enhance the taste or aroma of the formulation in liquid form. Suitable natural or synthetic flavoring agents can be selected from standard reference books, for example Fenaroli's Handbook of Flavor Ingredients, 3rd edition (1995). Non-limiting examples of suitable natural flavors, some of which can readily be simulated with synthetic agents or combinations thereof, include almond, anise, apple, apricot, bergamot, blackberry, blackcurrant, blueberry, cacao, caramel, cherry, cinnamon, clove, coffee, coriander, cranberry, cumin, dill, eucalyptus, fennel, fig, ginger, grape, grapefruit, guava, hop, lemon, licorice, lime, malt, mandarin, molasses, nutmeg, mixed berry, orange, peach, pear, peppermint, pineapple, raspberry, rose, spearmint, strawberry, tangerine, tea, vanilla, wintergreen, etc. Also useful, particularly where the formulation is intended primarily for pediatric use, is tutti-frutti or bubblegum flavor, a compounded flavoring agent based on fruit flavors. Presently preferred flavoring agents include anise,

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cinnamon, cacao, orange, peppermint, cherry (in particular wild cherry), grape, bubblegum, vanilla, and mixed berry. In some embodiments, the enalapril liquid formulation described herein comprises a mixed berry flavoring agent.

Flavoring agents can be used singly or in combinations of two or more.

In further embodiments, the enalapril liquid formulation comprises a coloring agent for identity and/or aesthetic purposes. Suitable coloring agents illustratively include FD&C Red No. 3, FD&C Red No. 20, FD&C Red No. 40, FD&C Yellow No. 6, FD&C Blue No. 2, FD&C Green No. 5, FD&C Orange No. 5, caramel, ferric oxide and mixtures thereof.

Thickeners impart viscosity or weight to the resultant liquid forms from the enalapril formulation described herein. Exemplary thickeners include dextrin, cellulose derivatives (carboxymethylcellulose and its salts, ethylcellulose, hydroxyethyl cellulose, methylcellulose, hypromellose, and the like) starches, pectin, polyethylene glycol, polyethylene oxide, trehalose and certain gums (xanthan gum, locust bean gum, etc.). In certain embodiments, the enalapril liquid formulation comprises a thickener.

Additional excipients are contemplated in the enalapril liquid formulation embodiments. These additional excipients are selected based on function and compatibility with the enalapril liquid formulations described herein and may be found, for example in *Remington: The Science and Practice of Pharmacy*. Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*. (Easton, Pa.: Mack Publishing Co 1975); Liberman, H. A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms* (New York, N.Y.: Marcel Dekker 1980); and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed (Lippincott Williams & Wilkins 1999), herein incorporated by reference in their entirety.

Stability

The main enalapril degradants are enalapril diketopiperazine and enalaprilat.

The enalapril oral liquid formulations described herein are stable in various storage conditions including refrigerated, ambient and accelerated conditions. Stable as used herein refers to enalapril oral liquid formulations having about 95% or greater of the initial enalapril amount and about 5% w/w or less total impurities or related substances at the end of a given storage period. The percentage of impurities is calculated from the amount of impurities relative to the amount of enalapril. Stability is assessed by HPLC or any other known testing method. In some embodiments, the stable enalapril oral liquid formulations have about 5% w/w, about 4% w/w, about 3% w/w, about 2.5% w/w, about 2% w/w, about 1.5% w/w, about 1% w/w, or about 0.5% w/w total impurities or related substances. In other embodiments, the stable enalapril oral liquid formulations have about 5% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 4% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 3% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 2% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 1% w/w total impurities or related substances.

At refrigerated condition, the enalapril oral liquid formulations described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 6 months, at least 9 months, at least 12 months, at least 15 months, at least 18

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months, at least 24 months, at least 30 months and at least 36 months. In some embodiments, refrigerated condition is $5\pm 3^\circ\text{C}$. In some embodiments, refrigerated condition is about 2°C ., about 2.1°C ., about 2.2°C ., about 2.3°C ., about 2.4°C ., about 2.5°C ., about 2.6°C ., about 2.7°C ., about 2.8°C ., about 2.9°C ., about 3°C ., about 3.1°C ., about 3.2°C ., about 3.3°C ., about 3.4°C ., about 3.5°C ., about 3.6°C ., about 3.7°C ., about 3.8°C ., about 3.9°C ., about 4°C ., about 4.1°C ., about 4.2°C ., about 4.3°C ., about 4.4°C ., about 4.5°C ., about 4.6°C ., about 4.7°C ., about 4.8°C ., about 4.9°C ., about 5°C ., about 5.1°C ., about 5.2°C ., about 5.3°C ., about 5.4°C ., about 5.5°C ., about 5.6°C ., about 5.7°C ., about 5.8°C ., about 5.9°C ., about 6°C ., about 6.1°C ., about 6.2°C ., about 6.3°C ., about 6.4°C ., about 6.5°C ., about 6.6°C ., about 6.7°C ., about 6.8°C ., about 6.9°C ., about 7°C ., about 7.1°C ., about 7.2°C ., about 7.3°C ., about 7.4°C ., about 7.5°C ., about 7.6°C ., about 7.7°C ., about 7.8°C ., about 7.9°C ., or about 8°C . At accelerated conditions, the enalapril oral liquid formulations described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months or at least 12 months. Accelerated conditions for the enalapril oral liquid formulations described herein include temperature and/or relative humidity (RH) that are at or above ambient levels (e.g. $25\pm 5^\circ\text{C}$.; $55\pm 10\%$ RH). In some instances, an accelerated condition is at about 25°C ., about 30°C ., about 35°C ., about 40°C ., about 45°C ., about 50°C ., about 55°C . or about 60°C . In other instances, an accelerated condition is above 55% RH, about 65% RH, about 70% RH, about 75% RH or about 80% RH. In further instances, an accelerated condition is about 40°C . or 60°C . at ambient humidity. In yet further instances, an accelerated condition is about 40°C . at $75\pm 5\%$ RH humidity.

Enalapril Oral Powder Formulation

In another aspect, enalapril oral liquid formulations described herein are prepared from the reconstitution of an enalapril powder formulation. In some embodiments, the enalapril powder formulation comprising enalapril, a sweetener, a preservative, and optionally an excipient is dissolved in water, a buffer, other aqueous solvent, or a liquid to form an enalapril oral liquid formulation. In one embodiment, the sweetening agent is sucralose. In one embodiment, the sweetener is not mannitol. In one embodiment, the sweetening agent is xylitol. In another embodiment, the preservative is sodium benzoate. In one embodiment, the preservative is a paraben preservative. In one aspect, the enalapril powder formulation described herein comprises enalapril, sucralose, and sodium benzoate. In some embodiments, the enalapril powder formulation herein further comprises a flavoring agent. In some embodiments, the enalapril powder formulation herein further comprises one or more buffering agents.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w to about 30% w/w of the powder formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w, about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about

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15.5% w/w, about 16% w/w, about 16.5% w/w, about 17% w/w, about 17.5% w/w, about 18% w/w, about 18.5% w/w, about 19% w/w, about 19.5% w/w, about 20% w/w, about 20.5% w/w, about 21% w/w, about 21.5% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5% w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the powder formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 10% w/w to about 25% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 13.5% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 19.5% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 24.5% w/w of the powder formulation. In some embodiments, enalapril is present in about 10.5% w/w of the powder formulation. In some embodiments, enalapril is present in about 14.5% w/w of the powder formulation. In some embodiments, enalapril is present in about 18% w/w of the powder formulation.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w to about 1% w/w of the powder formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w, about 0.15% w/w, about 0.2% w/w, about 0.25% w/w, about 0.3% w/w, about 0.35% w/w, about 0.4% w/w, about 0.45% w/w, about 0.5% w/w, about 0.55% w/w, about 0.6% w/w, about 0.65% w/w, about 0.7% w/w, about 0.75% w/w, about 0.8% w/w, about 0.85% w/w, about 0.9% w/w, about 0.95% w/w, or about 1% w/w of the powder formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.4% w/w to about 0.7% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 0.45% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 0.6% w/w of the powder formulation. In some embodiments, enalapril is present in about 0.4% w/w of the powder formulation. In some embodiments, enalapril is present in about 0.5% w/w of the powder formulation.

Various amounts and concentrations of other components (sweeteners, buffers, preservatives, and the like) in the enalapril powder formulations are found in the previous section describing the amounts and concentrations for the analogous enalapril oral liquid formulations. For example, in some embodiments where sucralose is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation; in an analogous enalapril powder formulation, sucralose would be about 1% w/w to about 30% w/w in the powder formulation. In some embodiments where sodium benzoate is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation, in an analogous enalapril powder formulation sodium benzoate is present in about 1% w/w to about 30% w/w in the powder formulation.

Liquid vehicles suitable for the enalapril powder formulations to be reconstituted into an oral solution described herein are selected for a particular oral liquid formulation (solution, suspension, etc.) as well as other qualities such as clarity, toxicity, viscosity, compatibility with excipients, chemical inertness, palatability, odor, color and economy. Exemplary liquid vehicles include water, ethyl alcohol, glycerin, propylene glycol, syrup (sugar or other sweetener based, e.g., Ora-Sweet® SF sugar-free flavored syrup), juices (apple, grape, orange, cranberry, cherry, tomato and the like), other beverages (tea, coffee, soft drinks, milk and

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the like), oils (olive, soybean, corn, mineral, castor and the like), and combinations or mixtures thereof. Certain liquid vehicles, e.g., oil and water, can be combined together to form emulsions. In some embodiments, water is used for as a vehicle for an enalapril oral liquid formulation. In other

embodiments, a syrup is used for as a vehicle for an enalapril oral liquid formulation. In yet other embodiments, a juice is used for as a vehicle for an enalapril oral liquid formulation. Buffering agents maintain the pH of the liquid enalapril formulation. Non-limiting examples of buffering agents include, but are not limited to sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium gluconate, aluminum hydroxide, aluminum hydroxide/sodium bicarbonate co precipitate, mixture of an amino acid and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer. Additional buffering agents include citric acid, sodium citrate, sodium tartrate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, sodium acetate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, and other calcium salts. Some buffering agents also impart effervescent qualities when a powder is reconstituted in a solution.

In some embodiments, the reconstituted oral liquid formulation comprises a buffer. In some embodiments, the buffer comprises citric acid and sodium citrate. In further embodiments, the enalapril powder formulation described herein comprises additional excipients including, but not limited to, glidants, flavoring agents, coloring agents and thickeners. Additional excipients such as bulking agents, tonicity agents and chelating agents are within the scope of the embodiments.

Glidants are substances that improve flowability of a powder. Suitable glidants include, but are not limited to, calcium phosphate tribasic, calcium silicate, cellulose (powdered), colloidal silicon dioxide, magnesium silicate, magnesium trisilicate, silicon dioxide, starch, talc and the like. In some embodiments, the enalapril powder formulations described herein comprise a glidant.

In another embodiment, the enalapril powder formulation described herein comprises a flavoring agent or flavorant to enhance the taste or aroma of the formulation in liquid form. Suitable natural or synthetic flavoring agents can be selected from standard reference books, for example Fenaroli's Handbook of Flavor Ingredients, 3rd edition (1995). Non-limiting examples of suitable natural flavors, some of which can readily be simulated with synthetic agents or combinations thereof, include almond, anise, apple, apricot, bergamot, blackberry, blackcurrant, blueberry, cacao, caramel, cherry, cinnamon, clove, coffee, coriander, cranberry, cumin, dill, eucalyptus, fennel, fig, ginger, grape, grapefruit, guava, hop, lemon, licorice, lime, malt, mandarin, molasses, nutmeg, mixed berry, orange, peach, pear, peppermint, pineapple, raspberry, rose, spearmint, strawberry, tangerine, tea, vanilla, wintergreen, etc. Also useful, particularly where the formulation is intended primarily for pediatric use, is tutti-frutti or bubblegum flavor, a compounded flavoring agent based on fruit flavors. Presently preferred flavoring agents include anise, cinnamon, cacao, orange, peppermint, cherry (in particular wild cherry), grape, bubblegum, vanilla, and

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mixed berry. Flavoring agents can be used singly or in combinations of two or more.

In further embodiments, the enalapril powder formulation described herein comprises a coloring agent for identity and/or aesthetic purposes. Suitable coloring agents illustratively include FD&C Red No. 3, FD&C Red No. 20, FD&C Red No. 40, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, caramel, ferric oxide and mixtures thereof.

In further embodiments, the enalapril powder formulation described herein comprises a thickener. Thickeners impart viscosity or weight to the resultant liquid forms from the enalapril formulation described herein. Exemplary thickeners include dextrin, cellulose derivatives (carboxymethylcellulose and its salts, ethylcellulose, hydroxyethyl cellulose, methylcellulose, hypromellose, and the like) starches, pectin, polyethylene glycol, polyethylene oxide, trehalose and certain gums (xanthan gum, locust bean gum, etc.).

Additional excipients are contemplated in the enalapril powder formulation embodiments. These additional excipients are selected based on function and compatibility with the the enalapril powder formulation described herein and may be found, for example in *Remington: The Science and Practice of Pharmacy*. Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*. (Easton, Pa.: Mack Publishing Co 1975); Liberman, H. A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms* (New York, N.Y.: Marcel Dekker 1980); and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed (Lippincott Williams & Wilkins 1999), herein incorporated by reference in their entirety.

In some embodiments, the enalapril oral liquid formulation prepared from the powder formulations described herein are homogenous. Homogenous liquids as used herein refer to those liquids that are uniform in appearance, identity, consistency and drug concentration per volume. Non-homogenous liquids include such liquids that have varied coloring, viscosity and/or aggregation of solid particulates, as well as non-uniform drug concentration in a given unit volume. Homogeneity in liquids are assessed by qualitative identification or appearance tests and/or quantitative HPLC testing or the like. The mixing methods and excipients described herein are selected to impart a homogenous quality to a resultant enalapril oral liquid formulation.

Mixing methods encompass any type of mixing that result in a homogenous enalapril oral liquid formulation. In some embodiments, a quantity of an enalapril powder formulation is added to a liquid vehicle and then mixed by a stirring, shaking, swirling, agitation element or a combination thereof. In certain instances, a fraction of a enalapril powder formulation (i.e., one-half, one-third, one-fourth, etc.) is added to a liquid vehicle, mixed by stirring, shaking, swirling, agitation or a combination thereof, and the subsequent powder fraction(s) is added and mixed. In other embodiments, a liquid vehicle is added to an enalapril powder formulation in a container, for example, a bottle, vial, bag, beaker, syringe, or the like. The container is then mixed by stirring, shaking, swirling, agitation, inversion or a combination thereof. In certain instances, a fractional volume of the liquid vehicle (i.e., one-half, one-third, one-fourth volume, etc.) is added to a enalapril powder formulation in a container, mixed by stirring, shaking, swirling, agitation, inversion or a combination thereof, and the subsequent liquid fraction(s) is added and mixed. In certain instances, a one-half fractional volume of the liquid vehicle is added to an enalapril powder formulation in a container and mixing by shaking; the other one-half fractional volume of the

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liquid vehicle is then subsequently added and mixed. In any of the above embodiments, mixing (i.e., stirring, shaking, swirling, agitation, inversion or a combination thereof) occurs for a certain time intervals such as about 10 seconds, about 20 seconds, about 30 seconds, about 45 seconds, about 60 seconds, about 90 seconds, about 120 seconds, about 2.5 minutes, about 3 minutes, about 3.5 minutes, about 4 minutes, or about 5 minutes. In embodiments, where there are two or more mixing steps, the time intervals for each mixing can be the same (e.g., 2x10 seconds) or different (e.g., 10 seconds for first mixing and 20 seconds for second mixing). In any of the above embodiments, a enalapril oral liquid formulation is allowed to stand for a period of time such as about 10 minutes, about 20 minutes, about 30 minutes, about 45 minutes, about 1 hour, about 1.5 hours or about 2 hours, to allow any air bubbles resultant from any of the mixing methods to dissipate.

Stability of Enalapril Powder Formulation

The enalapril powder formulations described herein are stable in various storage conditions including refrigerated, ambient and accelerated conditions. Stable as used herein refer to enalapril powder formulations having about 95% or greater of the initial enalapril amount and 5% w/w or less total impurities or related substances at the end of a given storage period. The percentage of impurities is calculated from the amount of impurities relative to the amount of enalapril. Stability is assessed by HPLC or any other known testing method. In some embodiments, the stable enalapril powder formulations have about 5% w/w, about 4% w/w, about 3% w/w, about 2.5% w/w, about 2% w/w, about 1.5% w/w, about 1% w/w, or about 0.5% w/w total impurities or related substances. In other embodiments, the stable enalapril powder formulations have about 5% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 4% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 3% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 2% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 1% w/w total impurities or related substances.

At refrigerated and ambient conditions, in some embodiments, the enalapril powder formulations described herein are stable for at least 1 week, 2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks, 16 weeks, 20 weeks, at least 24 weeks, at least 30 weeks, or at least 36 weeks. At accelerated conditions, in some embodiments, the enalapril powder formulations described herein are stable for at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks or at least 12 weeks. Accelerated conditions for the enalapril powder formulations described herein include temperature and/or relative humidity (RH) that are above ambient levels (e.g. 25±4° C.; 55±10% RH). In some instances, an accelerated condition is at about 30° C., about 35° C., about 40° C., about 45° C., about 50° C., about 55° C. or about 60° C. In other instances, an accelerated condition is above 65% RH, about 70% RH, about 75% RH or about 80% RH. In further instances, an accelerated condition is about 40° C. or 60° C. at ambient humidity. In yet further instances, an accelerated condition is about 40° C. at 75±5% RH humidity.

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Kits and Articles of Manufacture

For the enalapril powder and liquid formulations described herein, kits and articles of manufacture are also described. Such kits can comprise a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein including an enalapril powder or liquid formulation. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers can be formed from a variety of materials such as glass or plastic.

A kit will typically may comprise one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for an enalapril powder or liquid formulation described herein. Non-limiting examples of such materials include, but not limited to, buffers, diluents, filters, needles, syringes; carrier, package, container, vial and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use associated with an enalapril powder or liquid formulation. A set of instructions will also typically be included.

A label can be on or associated with the container. A label can be on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label can be associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. A label can be used to indicate that the contents are to be used for a specific therapeutic application. The label can also indicate directions for use of the contents, such as in the methods described herein.

Methods

Provided herein, in one aspect, are methods of treatment comprising administration of the enalapril oral liquid formulations described herein to a subject. In some embodiments, the enalapril oral liquid formulations described herein treat hypertension in a subject. Hypertension as used herein includes both primary (essential) hypertension and secondary hypertension. In certain instances, hypertension is classified in cases when blood pressure values are greater than or equal to 140/90 (systolic/diastolic) mm Hg in a subject. In certain instances, the enalapril oral liquid formulations described herein treat a subject having a blood pressure values are greater than or equal to 140/90 mm Hg. In certain instances, the enalapril oral liquid formulations described herein treat primary (essential) hypertension in a subject. In other instances, the enalapril oral liquid formulations described herein treat secondary hypertension in a subject.

In other embodiments, the enalapril oral liquid formulations described herein treat prehypertension in a subject. Prehypertension as used herein refers to cases where a subject's blood pressure is elevated above normal but not to the level considered to be hypertension. In some instances, prehypertension is classified in cases when blood pressure values are 120-139/80-89 mm Hg. In certain instances, the enalapril oral liquid formulations described herein treat a subject having blood pressure values of 120-139/80-89 mm Hg.

In yet other embodiments, the enalapril oral liquid formulations described herein are prophylactically administered to subjects suspected of having, predisposed to, or at risk of developing hypertension. In some embodiments, the administration of enalapril oral liquid formulations described herein allow for early intervention prior to onset

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of hypertension. In certain embodiments, upon detection of a biomarker, environmental, genetic factor, or other marker, the enalapril oral liquid formulations described herein are prophylactically administered to subjects.

In further embodiments, the enalapril oral liquid formulations described herein treat heart failure (e.g., symptomatic congestive), asymptomatic left ventricular dysfunction, myocardial infarction, diabetic nephropathy and chronic renal failure. In certain instances, the enalapril oral liquid formulations described herein treat symptomatic congestive heart failure. In other instances, the enalapril oral liquid formulations described herein treat asymptomatic left ventricular dysfunction. In further instances, the enalapril oral liquid formulations described herein treat myocardial infarction. In yet further instances, the enalapril oral liquid formulations described herein treat diabetic nephropathy. In yet further instances, the enalapril oral liquid formulations described herein treat chronic renal failure.

Dosing

In one aspect, the enalapril oral liquid formulations are used for the treatment of diseases and conditions described herein. In addition, a method for treating any of the diseases or conditions described herein in a subject in need of such treatment, involves administration of enalapril oral liquid formulations in therapeutically effective amounts to said subject.

Dosages of enalapril oral liquid formulations described can be determined by any suitable method. Maximum tolerated doses (MTD) and maximum response doses (MRD) for enalapril and/or enalaprilat can be determined via established animal and human experimental protocols as well as in the examples described herein. For example, toxicity and therapeutic efficacy of enalapril and/or enalaprilat can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between the toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD₅₀ and ED₅₀. Enalapril dosages exhibiting high therapeutic indices are of interest. The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED₅₀ with minimal toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. Additional relative dosages, represented as a percent of maximal response or of maximum tolerated dose, are readily obtained via the protocols.

In some embodiments, the amount of a given enalapril oral liquid formulation that corresponds to such an amount varies depending upon factors such as the particular enalapril salt or form, disease condition and its severity, the identity (e.g., weight, sex) of the subject or host in need of treatment, but can nevertheless be determined according to the particular circumstances surrounding the case, including, e.g., the specific agent being administered, the liquid composition type, the condition being treated, and the subject or host being treated.

In some embodiments, the enalapril oral liquid formulations described herein are provided in a dose per day from about 0.01 mg to 100 mg, from about 0.1 mg to about 80 mg, from about 1 to about 60, from about 2 mg to about 40 mg of enalapril. In certain embodiments, the enalapril oral liquid formulations described herein are provided in a daily dose of

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about 0.01 mg, about 0.05 mg, about 0.1 mg, about 0.2 mg, about 0.4 mg, about 0.6 mg, about 0.8 mg, about 1 mg, about 1.5 mg, about 2 mg, about 2.5 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 76 mg, about 80 mg, about 85 mg, about 90 mg or about 100 mg, or any range derivable therein. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 1 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 2 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 3 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 4 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 5 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 6 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 7 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 8 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 9 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 10 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 11 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 12 mg. The dose per day described herein can be given once per day or multiple times per day in the form of sub-doses given b.i.d., t.i.d., q.i.d., or the like where the number of sub-doses equal the dose per day.

In further embodiments, the daily dosages appropriate for the enalapril oral liquid formulations described herein are from about 0.01 to about 1.0 mg/kg per body weight. In one embodiment, the daily dosages appropriate for the enalapril oral liquid formulations are from about 0.02 to about 0.8 mg/kg enalapril per body weight. In another embodiment, the daily dosage appropriate for the enalapril oral liquid formulations are from about 0.05 to about 0.6 mg/kg per body weight. In another embodiment, the daily dosage appropriate for the enalapril oral liquid formulations is about 0.05 mg/kg, about 0.06 mg/kg, about 0.07 mg/kg, about 0.08 mg/kg, about 0.10 mg/kg, about 0.15 mg/kg, about 0.20 mg/kg, about 0.25 mg/kg, about 0.30 mg/kg, about 0.40 mg/kg, about 0.50 mg/kg, or about 0.60 mg/kg.

In other embodiments the enalapril oral liquid formulations are provided at the maximum tolerated dose (MTD) for enalapril and/or enalaprilat. In other embodiments, the amount of the enalapril oral liquid formulations administered is from about 10% to about 90% of the maximum tolerated dose (MTD), from about 25% to about 75% of the MTD, or about 50% of the MTD. In particular embodiments, the amount of the enalapril oral liquid formulations administered is from about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or higher, or any range derivable therein, of the MTD for enalapril and/or enalaprilat.

In further embodiments, the enalapril oral liquid formulations are provided in a dosage that is similar, comparable or equivalent to a dosage of a known enalapril tablet

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formulation. In other embodiments, the enalapril oral liquid formulations are provided in a dosage that provides a similar, comparable or equivalent pharmacokinetic parameters (e.g., AUC, C_{max} , T_{max} , C_{min} , $T_{1/2}$) as a dosage of a known enalapril tablet formulation. Similar, comparable or equivalent pharmacokinetic parameters, in some instances, refer to within 80% to 125%, 80% to 120%, 85% to 125%, 90% to 110%, or increments therein, of the given values. It should be recognized that the ranges can, but need not be symmetrical, e.g., 85% to 105%.

Administration

Administration of an enalapril oral liquid formulation is at a dosage described herein or at other dose levels and formulations determined and contemplated by a medical practitioner. In certain embodiments, the enalapril oral liquid formulations described herein are administered for prophylactic and/or therapeutic treatments. In certain therapeutic applications, the enalapril oral liquid formulations are administered to a patient already suffering from a disease, e.g., hypertension, in an amount sufficient to cure the disease or at least partially arrest or ameliorate the symptoms, e.g., lower blood pressure. Amounts effective for this use depend on the severity of the disease, previous therapy, the patient's health status, weight, and response to the enalapril formulations, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation clinical trial.

In prophylactic applications, the enalapril oral liquid formulations described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, e.g., hypertension. Such an amount is defined to be a "prophylactically effective amount or dose." In this use, the precise amounts also depend on the patient's state of health, weight, and the like. When used in a patient, effective amounts for this use will depend on the risk or susceptibility of developing the particular disease, previous therapy, the patient's health status and response to the enalapril formulations, and the judgment of the treating physician.

In certain embodiments wherein the patient's condition does not improve, upon the doctor's discretion the administration of an enalapril oral liquid formulations described herein are administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease. In other embodiments, administration of an enalapril oral liquid formulation continues until complete or partial response of a disease.

In certain embodiments wherein a patient's status does improve, the dose of an enalapril oral liquid formulation being administered may be temporarily reduced or temporarily suspended for a certain length of time (i.e., a "drug holiday"). In specific embodiments, the length of the drug holiday is between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, and 365 days. The dose reduction during a drug holiday is, by way of example only, by 10%-100%, including by way of example only 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 100%.

In some embodiments, enalapril oral liquid formulations described herein are administered chronically. For example, in some embodiments, an enalapril oral liquid formulation is administered as a continuous dose, i.e., administered daily to

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a subject. In some other embodiments, enalapril oral liquid formulations described herein are administered intermittently (e.g. drug holiday that includes a period of time in which the formulation is not administered or is administered in a reduced amount).

In some embodiments an enalapril oral liquid formulation is administered to a subject who is in a fasted state. A fasted state refers to a subject who has gone without food or fasted for a certain period of time. General fasting periods include at least 4 hours, at least 6 hours, at least 8 hours, at least 10 hours, at least 12 hours, at least 14 hours and at least 16 hours without food. In some embodiments, an enalapril oral liquid formulation is administered orally to a subject who is in a fasted state for at least 8 hours. In other embodiments, an enalapril oral liquid formulation is administered to a subject who is in a fasted state for at least 10 hours. In yet other embodiments, an enalapril oral liquid formulation is administered to a subject who is in a fasted state for at least 12 hours. In other embodiments, an enalapril oral liquid formulation is administered to a subject who has fasted overnight.

In other embodiments an enalapril oral liquid formulation is administered to a subject who is in a fed state. A fed state refers to a subject who has taken food or has had a meal. In certain embodiments, an enalapril oral liquid formulation is administered to a subject in a fed state 5 minutes post-meal, 10 minutes post-meal, 15 minutes post-meal, 20 minutes post-meal, 30 minutes post-meal, 40 minutes post-meal, 50 minutes post-meal, 1 hour post-meal, or 2 hours post-meal. In certain instances, an enalapril oral liquid formulation is administered to a subject in a fed state 30 minutes post-meal. In other instances, an enalapril oral liquid formulation is administered to a subject in a fed state 1 hour post-meal. In yet further embodiments, an enalapril oral liquid formulation is administered to a subject with food.

In further embodiments described herein, an enalapril oral liquid formulation is administered at a certain time of day for the entire administration period. For example, an enalapril oral liquid formulation can be administered at a certain time in the morning, in the evening, or prior to bed. In certain instances, an enalapril oral liquid formulation is administered in the morning. In other embodiments, an enalapril oral liquid formulation can be administered at different times of the day for the entire administration period. For example, an enalapril oral liquid formulation can be administered on 8:00 am in the morning for the first day, 12 pm noon for the next day or administration, 4 pm in the afternoon for the third day or administration, and so on.

Further Combinations

The treatment of certain diseases or conditions (e.g., hypertension, heart failure, myocardial infarction and the like) in a subject with an enalapril oral liquid formulation described herein encompass additional therapies and treatment regimens with other agents in some embodiments. Such additional therapies and treatment regimens can include another therapy, e.g., additional anti-hypertensives, for treatment of the particular disease or condition in some embodiments. Alternatively, in other embodiments, additional therapies and treatment regimens include other agents used to treat adjunct conditions associated with the disease or condition or a side effect from the enalapril oral liquid formulation in the therapy.

Additional agents for use in combination with an enalapril oral liquid formulation described herein include, but are not limited to, diuretics (loop, thiazide, potassium-sparing, and the like), beta blockers (metoprolol, propranolol, pronethalol, and the like), alpha blockers (phentolamine, phenoxyben-

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zamine, tamsulosin, prazosin, and the like), mixed alpha and beta blockers (bucindolol, carvedilol, labetalol), calcium channel blockers (dihydropyridines such as nifedipine, amlodipine, etc., diltiazem, verapamil and the like), angiotensin II receptor antagonists (saralasin, lsartan, eprosartin, irbesartan, valsartan, and the like), other ACE inhibitors (captopril, quinapril, ramipril, lisinopril, zofenopril, and the like), aldosterone antagonists (eplerenone, spironolactone and the like), vasodilators (hydralazine and the like) and alpha-2 agonists (clonidine, moxonidine, guanabenz and the like).

Certain Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments described herein, certain preferred methods, devices, and materials are now described.

As used herein and in the appended claims, the singular forms “a”, “an”, and “the” include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to “an excipient” is a reference to one or more excipients and equivalents thereof known to those skilled in the art, and so forth.

The term “about” is used to indicate that a value includes the standard level of error for the device or method being employed to determine the value. The use of the term “or” in the claims is used to mean “and/or” unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and to “and/or.” The terms “comprise,” “have” and “include” are open-ended linking verbs. Any forms or tenses of one or more of these verbs, such as “comprises,” “comprising,” “has,” “having,” “includes” and “including,” are also open-ended. For example, any method that “comprises,” “has” or “includes” one or more steps is not limited to possessing only those one or more steps and also covers other unlisted steps.

“Optional” or “optionally” may be taken to mean that the subsequently described structure, event or circumstance may or may not occur, and that the description includes instances where the events occurs and instances where it does not.

As used herein, the term “therapeutic” means an agent utilized to treat, combat, ameliorate, prevent or improve an unwanted condition or disease of a patient. In some embodiments, a therapeutic agent such as enalapril is directed to the treatment and/or the amelioration of, reversal of, or stabilization of the symptoms of hypertension described herein.

“Administering” when used in conjunction with a therapeutic means to administer a therapeutic systemically or locally, as directly into or onto a target tissue, or to administer a therapeutic to a patient whereby the therapeutic positively impacts the tissue to which it is targeted. Thus, as used herein, the term “administering”, when used in conjunction with an enalapril formulation, can include, but is not limited to, providing an enalapril formulation into or onto the target tissue; providing an enalapril formulation systemically to a patient by, e.g., oral administration whereby the therapeutic reaches the target tissue or cells. “Administering” a formulation may be accomplished by injection, topical administration, and oral administration or by other methods alone or in combination with other known techniques.

The term “animal” as used herein includes, but is not limited to, humans and non-human vertebrates such as wild, domestic and farm animals. As used herein, the terms

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“patient,” “subject” and “individual” are intended to include living organisms in which certain conditions as described herein can occur. Examples include humans, monkeys, cows, sheep, goats, dogs, cats, mice, rats, and transgenic species thereof. In a preferred embodiment, the patient is a primate. In certain embodiments, the primate or subject is a human. In certain instances, the human is an adult. In certain instances, the human is child. In further instances, the human is 12 years of age or younger. In certain instances, the human is elderly. In other instances, the human is 60 years of age or older. Other examples of subjects include experimental animals such as mice, rats, dogs, cats, goats, sheep, pigs, and cows. The experimental animal can be an animal model for a disorder, e.g., a transgenic mouse with hypertensive pathology. A patient can be a human suffering from hypertension, or its variants or etiological forms.

By “pharmaceutically acceptable”, it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The term “pharmaceutical composition” shall mean a composition comprising at least one active ingredient, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

A “therapeutically effective amount” or “effective amount” as used herein refers to the amount of active compound or pharmaceutical agent that elicits a biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following: (1) preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease, (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology), and (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology). As such, a non-limiting example of a “therapeutically effective amount” or “effective amount” of a formulation of the present disclosure may be used to inhibit, block, or reverse the activation, migration, or proliferation of cells or to effectively treat hypertension or ameliorate the symptoms of hypertension.

The terms “treat,” “treated,” “treatment,” or “treating” as used herein refers to both therapeutic treatment in some embodiments and prophylactic or preventative measures in other embodiments, wherein the object is to prevent or slow (lessen) an undesired physiological condition, disorder or disease, or to obtain beneficial or desired clinical results. For the purposes described herein, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of the condition, disorder or disease; stabilization (i.e., not worsening) of the state of the condition, disorder or disease; delay in onset or slowing of the progression of the condition, disorder or disease; amelioration of the condition, disorder or disease state; and remission (whether partial or total), whether detectable or

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undetectable, or enhancement or improvement of the condition, disorder or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment. A prophylactic benefit of treatment includes prevention of a condition, retarding the progress of a condition, stabilization of a condition, or decreasing the likelihood of occurrence of a condition. As used herein, "treat," "treated," "treatment," or "treating" includes prophylaxis in some embodiments.

EXAMPLES

Example A: Effect of pH on the Formation of Degradants in Enalapril Formulations at 60° C.

Formulations were prepared containing enalapril maleate according to Table A-1. The pH of each solution was recorded. Five milliliters of each formulation were transferred to each of four 3-dram glass screw-capped vials with Teflon inserts in the caps. The vials were placed into a 60° C. heating chamber then one vial removed and analyzed by HPLC at times of zero, ~97 and ~180 hours.

TABLE A-1

Formulation (in mg/mL) of Enalapril Formulations at Varying pH and Citrate Buffer Concentration						
Component	Formulation (mM citrate)					
	A1 (50)	A2 (50)	A3 (50)	A4 (50)	A5 (50)	A6 (25)
Enalapril maleate	1.0	1.0	1.0	1.0	1.0	1.0
Mannitol	50	50	50		50	6.0
Xylitol				50		
Citric acid, anhydrous	7.35	5.05	2.55	5.05	5.05	2.76
Sodium citrate, dihydrate	3.45	7.0	10.8	7.0	7.0	3.15
Sodium benzoate	1	1	1	1	1	
Methylparaben sodium					1.75	0.335
Propylparaben sodium						0.095
Potassium sorbate						1
Sucralose	0.75	0.75	0.75	0.75	0.75	0.75
Silicon dioxide						0.075
Mixed berry flavor (powdered)	0.5	0.5	0.5	0.5	0.5	0.5
Water	qs	qs	qs	qs	qs	qs
pH	3.4	4.4	5.2	4.4	4.5	4.4

qs = sufficient quantity

The results of the HPLC analysis for the two main degradants in the samples, enalapril diketopiperazine and enalaprilat, are provided in Table A-2.

TABLE A-2

Primary Degradants Present in the Formulations (% w/w of enalapril maleate)						
Hours at 60° C.	Formulation					
	A1	A2	A3	A4	A5	A6
Enalapril Diketopiperazine						
0	0.04	0.03	0.03	0.03	0.03	0.03
97	3.10	0.88	0.33	0.86	0.70	0.53
180	6.21	1.77	0.75	1.73	1.43	1.07
Enalaprilat						
0	0.09	0.15	0.29	0.14	0.16	0.12
97	5.20	16.9	47.4	16.1	20.3	15.6
180	9.94	34.8	113	33.5	42.2	31.7

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Example B: Effect of Buffer Concentration on the Formation of Degradants in Enalapril Formulations at 60° C.

Formulations were prepared containing enalapril maleate according to Table B-1. The pH of each solution was measured and adjusted as needed to pH 3.3 with ~1N HCl or ~0.5N NaOH. Five milliliters of each formulation were transferred to each of six 3-dram glass screw-capped vials with Teflon inserts in the caps. The vials were placed into a 60° C. heating chamber then two vials were removed and analyzed by HPLC at times of zero, ~66 and ~139 hours.

TABLE B-1

Formulation (in mg/mL) of Enalapril Maleate Formulations at Varying Citrate Buffer Concentrations			
Component	Formulation		
	B1 (5 mM citrate)	B2 (10 mM citrate)	B3 (20 mM citrate)
Enalapril maleate	1.0	1.0	1.0
Citric acid, anhydrous	0.82	1.65	3.29

TABLE B-1-continued

Formulation (in mg/mL) of Enalapril Maleate Formulations at Varying Citrate Buffer Concentrations			
Component	Formulation		
	B1 (5 mM citrate)	B2 (10 mM citrate)	B3 (20 mM citrate)
Sodium citrate, anhydrous	0.19	0.38	0.75
Sodium benzoate	1.0	1.0	1.0
Sucralose	0.7	0.7	0.7
Mixed berry flavor (powdered)	0.5	0.5	0.5
Water	qs	qs	qs
pH	3.3	3.3	3.3

qs = sufficient quantity

The results of the HPLC analysis for the two main degradants in the samples, enalapril diketopiperazine and enalaprilat, are provided in Table B-2.

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TABLE B-2

Primary Degradants Present in the Formulations (% w/w of enalapril maleate)			
Hours	Formulation		
at 60° C.	B1 (5 mM citrate)	B2 (10 mM citrate)	B3 (20 mM citrate)
Enalapril Diketopiperazine			
0	0.01	0.01	0.01
66	1.57	1.63	1.79
139	3.70	3.94	4.24
Enalaprilat			
0	0.00	0.00	0.00
66	2.98	2.88	3.19
139	5.28	5.23	5.69

Example C: Stability of Enalapril Maleate Formulations Containing Paraben Preservatives

Powder formulations were prepared according to Table C-1. All components in each formulation except mannitol or xylitol were added to a 2.5 liter polypropylene screw capped bottle. The bottle was mixed by inversion in a Turbula® mixer for 5 minutes. The mannitol or xylitol was then added and the components mixed for 5 minutes, then the other half of the mannitol or xylitol was added and a final mix of 5 minutes was completed.

One liter of solution formulation was prepared for each formulation by adding an appropriate amount of each powdered formulation to a 1 liter volumetric flask and adding about 500 mL water. The powder was dissolved with mixing then the contents of the flask were brought to 1 liter with additional water. The amount of powder to add was determined such that the final concentration of enalapril maleate was 1.0 mg/mL. Fifty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5° C.±3° C., at room temperature (19-23° C.) and at 40° C.±2° C. At various times, bottles were removed from the storage condition and analyzed.

TABLE C-1

Composition of Enalapril Maleate Formulations					
Component	C1	C2	C3	C4	C5
Powder Formulation (grams)					
Enalapril maleate	12.3	12.3	8.86	2.16	2.16
Mannitol	74.4	74.4	394.0		
Xylitol				96.6	93.7
Citric acid, anhydrous	28.6	35.6	28.4	5.40	5.40
Sodium citrate, anhydrous	24.5	14.7	7.73	4.10	4.10
Sodium methylparaben	4.17	4.17	8.86	2.16	2.16
Sodium propylparaben	1.10	1.10			
Potassium sorbate	12.3	12.3			
Sodium benzoate			8.86	2.16	2.16
Xanthan Gum					1.62
Colloidal silicon dioxide	0.859	0.859	4.43		1.08
Sucralose	9.20	9.20	6.64	1.62	1.62
Mixed berry flavor	6.13	6.13	4.43	1.08	1.08
Total solids	173.5	170.7	472.3	115.2	115.2
Liquid Formulations (mg/mL)					
Enalapril maleate	1.00	1.00	1.00	1.00	1.00
Mannitol	6.07	6.07	44.5		

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TABLE C-1-continued

Composition of Enalapril Maleate Formulations					
Component	C1	C2	C3	C4	C5
Xylitol				44.7	43.4
Citric acid, anhydrous	2.33	2.90	3.21	2.50	2.50
Sodium citrate, anhydrous	2.00	1.20	0.87	1.90	1.90
Sodium methylparaben	0.34	0.34	1.00	1.00	1.00
Sodium propylparaben	0.09	0.09	1.00		
Potassium sorbate	1.00	1.00			
Sodium benzoate			1.00	1.00	1.00
Xanthan Gum					0.75
Colloidal silicon dioxide	0.07	0.07	0.50		0.50
Sucralose	0.75	0.75	0.75	0.75	0.75
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50
pH (measured)	4.4	3.8	3.7	4.4	4.6

The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table C-2.

TABLE C-2

Degradant Content After Storage (% w/w of enalapril maleate)								
25		Storage		Formulation				
		° C.	Weeks	C1	C2	C3	C4	C5
Liquid Formulations								
30	Diketopiperazine	5	0	0.03	0.04	0.04	0.02	0.02
			4	0.02	0.03	0.03	0.03	0.02
		19-23	8	0.03	0.04	0.04		
			0	0.03	0.04	0.04	0.02	0.02
	4		0.05	0.09	0.11	0.05	0.04	
	8		0.08	0.17	0.19			
	35	40	0	0.03	0.04	0.04	0.02	0.02
			4	0.35	0.91	1.10	0.31	0.21
Enalaprilat		5	8	0.65	1.80	2.05		
			0	0.18	0.14	0.12	0.13	0.19
	4		0.18	0.15	0.12	0.43	0.53	
	8		0.55	0.38	0.34			
	19-23	0	0.18	0.14	0.12	0.13	0.19	
		4	1.35	0.83	0.80	1.75	2.29	
		8	3.34	2.06	1.98			
		0	0.18	0.14	0.12	0.13	0.19	
	40	40	4	10.49	6.08	6.11	12.30	16.14
			8	24.37	14.12	14.22		

Example D: Stability of Enalapril Maleate Formulations Containing Benzoate Preservative

Powder formulations were prepared according to Table D-1. All components in each formulation except enalapril maleate and mannitol or xylitol were blended with a mortar and pestle. The enalapril maleate was then triturated with the blend. The xylitol or mannitol was then triturated into the blend using a geometric dilution technique.

One liter of solution formulation was prepared for each formulation by adding an appropriate amount of each powdered formulation to a 1 liter volumetric flask and adding about 500 mL water. The powder was dissolved with mixing then the contents of the flask were brought to 1 liter with additional water. The amount of powder to add was determined such that the final concentration of enalapril maleate was 1.0 mg/mL. Fifty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5° C.±3° C., at room temperature (19-23° C.) and at 40° C.±2° C. At various times, bottles were removed from the storage condition and analyzed.

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TABLE D-1

Composition of Enalapril Maleate Formulations						
Component	D1	D2	D3	D4	D5	D6
Powder Formulation (grams)						
Enalapril maleate	3.63	3.63	3.63	3.63	8.86	2.16
Xylitol	537.2	176.1		537.2		
Mannitol			319.4		401.2	98.9
Citric acid, anhydrous	11.9	11.9	11.9	10.4	26.6	6.48
Sodium citrate, anhydrous	2.72	2.72	2.72	4.86	11.3	2.76
Sodium benzoate	3.63	3.63	3.63	3.63	8.86	2.16
Rebalance X60 (sucralose and maltodextrin)		10.9				
Sucralose					6.64	1.62
Saccharin sodium			7.26			
Colloidal silicon dioxide					4.43	
Mixed berry flavor	1.82	1.82	1.82	1.82	4.43	1.08
Total solids	561	211	350.	561	472.3	115.2
Liquid Formulations (mg/mL)						
Enalapril maleate	1.00	1.00	1.00	1.00	1.00	1.00
Xylitol	148.0	48.5		148.0		
Mannitol			88.0		45.3	45.8
Citric acid, anhydrous	3.29	3.29	3.29	2.85	3.00	3.00
Sodium citrate, anhydrous	0.75	0.75	0.75	1.34	1.28	1.28
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00
Rebalance X60 (sucralose and maltodextrin)		3.00				
Sucralose					0.75	0.75
Saccharin sodium			2.00			
Colloidal silicon dioxide					0.50	
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50	0.50
pH (measured)	3.2	3.2	3.4	3.7	3.6	3.6

The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table D-2.

TABLE D-2

Degradant Content After Storage (% w/w of enalapril maleate)								
		Storage		Formulation				
		° C.	Weeks	D1	D2	D3	D4	D5
Liquid Formulations								
Diketopiperazine	5	0	0.04	0.02	0.03	0.03	0.04	0.04
		4	0.07	0.03	0.05	0.05	0.03	
		8	0.11	0.06	0.08	0.08	0.05	
		12	0.08	0.04	0.06	0.06		
		26	0.11	0.07	0.09	0.07		
	19-23	0	0.04	0.02	0.03	0.03	0.04	0.04
		4	0.27	0.21	0.24	0.16	0.12	0.12
		8	0.50	0.41	0.47	0.30	0.21	0.22
		12	0.62	0.52	0.58	0.35		
		26	1.39	1.20	1.33	0.76		
	40	0	0.04	0.02	0.03	0.03	0.04	0.04
		4	2.87	2.32	2.73	1.57	1.21	1.13
		8	5.13	4.42	5.44	2.97	2.23	2.16
		12	6.86	5.90	6.90	3.91		
		26	13.63	12.18	13.56	7.74		
Enalaprilat	5	0	0.03	0.02	0.03	0.03	0.13	0.14
		4	0.15	0.12	0.06	0.17	0.13	
		8	0.22	0.19	0.22	0.27	0.34	
		12	0.20	0.17	0.19	0.22		
		8	0.32	0.30	0.30	0.39		
	19-23	0	0.03	0.02	0.03	0.03	0.13	0.14
		4	0.69	0.66	0.69	0.86	0.74	0.76
		8	1.38	1.33	1.41	1.68	1.83	1.82
		12	1.71	1.68	1.73	2.15		
		26	3.63	3.61	3.59	4.55		

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TABLE D-2-continued

Degradant Content After Storage (% w/w of enalapril maleate)							
Storage		Formulation					
° C.	Weeks	D1	D2	D3	D4	D5	D6
40	0	0.03	0.02	0.03	0.03	0.13	0.14
	4	4.76	4.42	4.76	6.45	5.55	5.24
	8	8.95	8.64	9.61	12.94	12.73	12.18
	12	11.01	10.64	11.41	16.16		
	26	17.18	17.11	18.30	27.36		

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Example E: Stability of Solution Formulations of
Enalapril Maleate

Solution formulations were prepared according to Table E-1. Thirty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5° C.±3° C., at room temperature (19-23° C.) and at 40° C.±2° C. At various times, bottles were removed from the storage condition and analyzed.

Composition of Enalapril Maleate Formulations (mg/mL)						
Component	E1	E2	E3	E4	E5	E6
Enalapril maleate	1.00	1.00	1.00	1.00	1.00	1.00
Xylitol	150	200		150		

-continued

Composition of Enalapril Maleate Formulations (mg/mL)						
Component	E1	E2	E3	E4	E5	E6
Citric acid anhydrous	3.29	3.29	3.29	3.29	1.65	0.82
Sodium citrate anhydrous	0.75	0.75	0.75	0.75	0.38	0.19
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00
Sucralose			0.70		0.70	0.70
Mixed berry flavor	0.50		0.50	0.50	0.50	0.50
Water	qs	qs	qs	qs	qs	qs
pH (measured)	3.3	3.3	3.3	3.4	3.3	3.3

qs = sufficient quantity

The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table E-2.

TABLE E-2

Degradant Content After Storage (% w/w of enalapril maleate)							
	Storage		Formulation				
	° C.	Weeks	E1	E2	E3	E4	E6
Diketopiperazine	5	0	0.01	0.01	0.01	0.01	0.01
		4	0.04	0.04	0.05	0.04	0.03
		8	0.04	0.04	0.04	0.04	0.03
		12	0.05	0.05	0.04	0.05	0.04
		26	0.07	0.06	0.05	0.06	0.05
		52					0.15
	19-23	62	0.18	0.18	0.16	0.14	
		0	0.01	0.01	0.01	0.01	0.01
		4	0.22	0.23	0.21	0.20	0.16
		8	0.35	0.35	0.32	0.31	0.29
		12	0.58	0.59	0.53	0.51	0.48
		26	1.10	1.10	1.00	0.95	0.97
		52					2.30
	40	62	3.02	3.04	2.75	2.64	
		0	0.01	0.01	0.01	0.01	0.01
		4	2.65	2.71	2.60	2.42	1.76
		8	4.02	3.99	3.99	3.62	3.37
		12	6.72	6.42	6.47	6.00	5.53
		26					5.29
Enalaprilat	5	0	0.00	0.00	0.01	0.02	0.00
		4	0.07	0.09	0.10	0.11	0.07
		8	0.12	0.14	0.10	0.13	0.09
		12	0.16	0.15	0.15	0.17	0.14
		26	0.31	0.30	0.29	0.31	0.27
		52					0.54
	19-23	62	0.75	0.75	0.74	0.71	
		0	0.00	0.00	0.01	0.02	0.00
		4	0.65	0.65	0.68	0.70	0.50
		8	1.17	1.19	1.20	1.23	1.03
		12	1.67	1.69	1.72	1.80	1.30
		26	3.36	3.38	3.42	3.57	3.07
	40	52					6.32
		62	7.99	8.02	8.04	8.57	5.88

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TABLE E-2-continued

Degradant Content After Storage (% w/w of enalapril maleate)							
Storage		Formulation					
° C.	Weeks	E1	E2	E3	E4	E5	E6
40	0	0.00	0.00	0.01	0.02	0.00	0.00
	4	4.85	4.93	5.19	5.42	3.33	3.25
	8	8.08	8.06	8.56	9.01	6.65	6.35
	12	10.70	10.48	11.01	11.97	8.14	7.96

Example F: Effect of pH on the Formation of Degradants in Enalapril Formulations at 5° C. and 19-23° C.

The content of enalapril diketopiperazine and enalaprilat that were formed after 8 weeks of storage for formulations C1-C3 and D1-D5 are plotted in FIG. 1 (5° C. ±3° C.) and FIG. 2 (19-23° C. storage). These formulations all contained 20 mM total citrate buffer content, but with varying pH. The general effects of formulation pH on the formation of the two main enalapril degradants are shown.

Example G: Antimicrobial Effectiveness Testing of Enalapril Maleate Formulations at pH 3.3

Enalapril formulations were prepared containing differing amounts of the antimicrobial preservative, sodium benzoate. The formulations were then tested for antimicrobial effectiveness (AET) according to the procedures in the 2014 United States Pharmacopeia 37, Chapter <51> for category 3 products. The formulation of the formulations and the AET results are included in Table G-1.

TABLE G-1

Formulation and AET Testing Results					
	Formulation				
	G1	G2	G3	G4	G5
Formulation (mg/mL)					
Enalapril maleate	1.00	1.00	1.00	1.00	1.00
Xylitol	150	150	150	150	
Sucralose					0.70
Citric acid, anhydrous	1.64	1.64	1.64	1.64	1.80
Sodium citrate, anhydrous	0.322	0.322	0.322	0.322	
Sodium citrate, dihydrate					0.165
Sodium benzoate	1.00	0.80	0.60	0.40	1.0
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50
Water	q.s.	q.s.	q.s.	q.s.	q.s.
HCl/NaOH	as need to achieve pH				
Measured pH	3.3	3.3	3.3	3.3	3.3
AET Results					
USP <51>	Pass	Pass	Pass	Pass	Pass

qs = sufficient quantity

Example H: Clinical Trial: Bioavailability Study of 10 mg Enalapril Maleate Oral Solution Vs. 10 mg Epaned® Powder for Oral Solution (Reconstituted) Under Fasted Conditions

The objective of this open-label, randomized, two-period, two-treatment, two-way crossover study was to compare the oral bioavailability of a test formulation of 10 mL of enalapril maleate oral solution, 1 mg/mL (formulation E-5),

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to an equivalent oral dose of the commercially available comparator product, Epaned® (enalapril maleate) Powder for Oral Solution, 1 mg/mL, when administered under fasted conditions in healthy adults.

Study design: Thirty-two healthy adult subjects received a single 10 mL dose of enalapril maleate oral solution, 1 mg/mL, formulation E-5 (Treatment A), in one period and a separate single dose of Epaned Powder for Oral Solution (reconstituted with the supplied Ora-Sweet SF), 1 mg/mL (Treatment B) in another period. Each treatment was administered after an overnight fast of at least 10 hours, followed by a 4-hour fast postdose. Each treatment was administered via a 10 mL oral dosing syringe and followed with 240 mL of room temperature tap water. Each drug administration was separated by a washout period of at least 7 days.

During each study period, meals were the same and scheduled at approximately the same times relative to dose. In addition, during each period, blood samples were obtained prior to and following each dose at selected times through 72 hours postdose. Pharmacokinetic samples were analyzed for enalapril and its metabolite enalaprilat using a validated analytical method; appropriate pharmacokinetic parameters were calculated for each formulation using non-compartmental methods. Blood was also drawn and urine collected for clinical laboratory testing at screening and at the end of the study.

Statistical Methods: The concentration-time data were analyzed using noncompartmental methods in Phoenix™ WinNonlin® (Version 6.3, Pharsight Corporation). Concentration-time data that were below the limit of quantitation (BLQ) were treated as zero in the data summarization and descriptive statistics. In the pharmacokinetic analysis, BLQ concentrations were treated as zero from time-zero up to the time at which the first quantifiable concentration was observed; embedded and/or terminal BLQ concentrations were treated as “missing”. Actual sample times were used for all pharmacokinetic and statistical analyses. Analysis of variance (ANOVA) and the Schirmann’s two one-sided t-test procedures at the 5% significance level were applied to the log-transformed pharmacokinetic exposure parameters, C_{max} , AUC_{last} , and AUC_{inf} . The 90% confidence interval for the ratio of the geometric means (Test/Reference) was calculated. Bioequivalence was declared if the lower and upper confidence intervals (CIs) of the log-transformed parameters were within 80% to 125% for enalapril and enalaprilat.

Results: A total of 32 subjects participated in the study and 29 of these subjects completed both study periods. Based on the geometric mean ratios of enalapril and enalaprilat AUCs (AUC_{last} and AUC_{inf}), the bioavailability of the enalapril maleate oral solution (formulation E-5) relative to the Epaned Powder for Oral Solution (reconstituted) was approximately 105% to 110%. The geometric mean ratios of enalapril and enalaprilat C_m were approximately 115% and

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109%, respectively. The 90% CI for comparing the maximum exposure to enalapril and enalaprilat, based on $\ln(C_{max})$, was within the accepted 80% to 125% limits. The 90% CIs for comparing total systemic exposure to enalapril and enalaprilat, based on $\ln(AUC_{last})$ and $\ln(AUC_{inf})$, was within the accepted 80% to 125% limits. Therefore, the test formulation of enalapril maleate oral solution, 1 mg/mL, is bioequivalent to the reference product, Epaned Powder for Oral Solution (reconstituted), 1 mg/mL, under fasted conditions.

While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

What is claimed is:

1. An oral liquid formulation, comprising:
 - (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
 - (ii) a buffer comprising a mixture of citric acid and sodium citrate, wherein the buffer is present at a concentration between about 5 mM and about 20 mM in the oral liquid formulation;
 - (iii) about 1 mg/ml sodium benzoate; and
 - (iv) water;
 wherein the formulation maintains about 95% w/w or greater of the initial enalapril amount at the end of a storage period of at least 12 months at about $5\pm 3^\circ\text{C}$.
2. The oral liquid formulation of claim 1 further comprising a sweetener.
3. The oral liquid formulation of claim 2, wherein the sweetener is sucralose.
4. The oral liquid formulation of claim 1 further comprising a flavoring agent.
5. The oral liquid formulation of claim 1, wherein the formulation does not contain mannitol.
6. The oral liquid formulation of claim 1, wherein the formulation does not contain silicon dioxide.
7. The oral liquid formulation of claim 1, wherein the buffer comprises about 0.8 to about 3.5 mg/ml citric acid.
8. The oral liquid formulation of claim 1, wherein the buffer comprises about 0.1 to about 0.8 mg/ml sodium citrate.
9. The oral liquid formulation of claim 1, wherein the pH of the oral liquid formulation is less than about 3.5.
10. The oral liquid formulation of claim 1, wherein the pH of the oral liquid formulation is between about 3 and about 3.5.
11. The oral liquid formulation of claim 1, wherein the pH of the oral liquid formulation is about 3.3.
12. The oral liquid formulation of claim 1, wherein the formulation maintains about 95% w/w or greater of the initial enalapril amount at the end of a storage period of at least 18 months at about $5\pm 3^\circ\text{C}$.
13. An oral liquid formulation, consisting essentially of:
 - (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;

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(ii) a buffer comprising a mixture of citric acid and sodium citrate, wherein the buffer is present at a concentration between about 5 mM and about 20 mM in the oral liquid formulation;

(iii) about 1 mg/ml sodium benzoate;

(iv) water; and

(v) optionally a sweetener, a flavoring agent, or both; wherein the formulation maintains about 95% w/w or greater of the initial enalapril amount at the end of a storage period of at least 12 months at about $5\pm 3^\circ\text{C}$.

14. An oral liquid formulation, comprising:

(i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;

(ii) a buffer comprising a mixture of citric acid and sodium citrate, wherein the buffer is present at a concentration between about 5 mM and about 20 mM in the oral liquid formulation;

(iii) about 1 mg/ml of a preservative, wherein the preservative is a paraben or a mixture of parabens; and

(iv) water;

wherein the formulation maintains about 95% w/w or greater of the initial enalapril amount at the end of a storage period of at least 12 months at about $5\pm 3^\circ\text{C}$.

15. The oral liquid formulation of claim 14 further comprising a sweetener.

16. The oral liquid formulation of claim 15, wherein the sweetener is sucralose.

17. The oral liquid formulation of claim 14 further comprising a flavoring agent.

18. The oral liquid formulation of claim 14, wherein the formulation does not contain mannitol.

19. The oral liquid formulation of claim 14, wherein the formulation does not contain silicon dioxide.

20. The oral liquid formulation of claim 14, wherein the pH of the oral liquid formulation is less than about 3.5.

21. The oral liquid formulation of claim 14, wherein the pH of the oral liquid formulation is between about 3 and about 3.5.

22. The oral liquid formulation of claim 14, wherein the pH of the oral liquid formulation is about 3.3.

23. The oral liquid formulation of claim 14, wherein the formulation maintains about 95% w/w or greater of the initial enalapril amount at the end of a storage period of at least 18 months at about $5\pm 3^\circ\text{C}$.

24. The oral liquid formulation of claim 1, wherein the enalapril or a pharmaceutically acceptable salt or solvate thereof is enalapril maleate, and wherein the enalapril maleate is present in the oral liquid formulation at about 1.0 mg/ml.

25. The oral liquid formulation of claim 1, wherein the buffer is present at a concentration between about 10 mM and about 20 mM in the oral liquid formulation.

26. The oral liquid formulation of claim 1, wherein the buffer is present at a concentration of about 10 mM in the oral liquid formulation.

27. The oral liquid formulation of claim 14, wherein the enalapril or a pharmaceutically acceptable salt or solvate thereof is enalapril maleate, and wherein the enalapril maleate is present in the oral liquid formulation at about 1.0 mg/ml.

28. The oral liquid formulation of claim 14, wherein the buffer is present at a concentration between about 10 mM and about 20 mM in the oral liquid formulation.

* * * * *

EXHIBIT 26

OPTINEB®-ir

Microprocessor Controlled • Mobile Ultrasonic Nebuliser

Microprocessor Controlled Mobile Ultrasonic Nebuliser

Operating Instructions

Operating Instructions

for Artificial Respiration (ventilation)

for physicians and authorized clinic personnel/
for physicians and authorized clinic personnel



Unit Type
ON-100/2-2.4 MHz
Made in Germany/
Made in Germany

NEBU-TEC med. Produkte

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OPTINEB®-ir

Microprocessor Controlled Mobile Ultrasonic Nebuliser

Operating Instructions

Type: ON-100/2-2.4 MHz

Made in Germany

Dear Patient,

With the mobile Ultrasonic Nebuliser **OPTINEB®-ir**, you have received an inhalation device that has been adjusted extremely precisely in a conditioned room. In order to ensure a constant operation of the equipment we ask you to carefully read the operating manual and to follow the instructions before you put the device into service.

We wish you every success for your treatment with the **OPTINEB®-ir**



OPTINEB®-ir

Microprocessor Controlled Mobile Ultrasonic Nebuliser

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1.0 Symbols



Attention, see instructions



Protection class II device



Applied part, type B



Device class AP



1275

2.0 Safety Instructions

These operating instructions must be fully understood and observed when using this device. In all cases the operator is liable for the safe operation of the device if it is used by a third party or not used according to the instructions. Important information is highlighted by the following terms:

WARNING

Important safety information on hazards that can lead to bodily harm.

ATTENTION

Important information on operating procedures that can cause device malfunctions.

CAUTION

Information that prevents product damage.

NOTE

Information that you should be especially aware of.
[For component parts, see Sketch 4.0]

Please read through the instructions for use carefully before initial operation.
Keep these operating instructions in a safe place.

WARNING

1. Pull out the mains plug after each use.
2. Do not use the device while bathing.
3. The device is to be set up so that it cannot fall into water.
4. Do not immerse the device into water or any other fluid.
5. Do not use the device if it has fallen into water, and immediately pull out the mains plug.
6. Do not use the device in the rain.
7. Do not use the device near easily inflammable materials.
8. Never place your hand or finger in the medication reservoir while the device is operating.

ATTENTION

1. An operating electrical device should never be left unattended.
2. You must be particularly careful when the device is used by or near children or seriously ill persons.
3. Only use the device for its intended purpose, as specified in these operating instructions. Under no circumstances should accessory parts be used that are not recommended by the manufacturer.
4. Never operate this device in the following cases:
 - a) if the mains cable or plug is damaged
 - b) if the device is not properly functioning
 - c) if the device was dropped or was damaged
 - d) if the device fell into water. In such cases, send the device to the manufacturer or to an authorized NEBU-TEC dealer for inspection and repair.
5. Keep the mains cable away from heated surfaces.
6. Place the device on a level and stable surface in a way that no air openings are blocked.
7. Do not use the device while sleeping.
8. Never clean the ultrasonic nebulizer in the dishwasher or microwave (never expose the base unit to direct microwave radiation).
9. While cleaning the contact fluid chamber of the **OPTINEB®-ir**, prevent moisture from being able to penetrate into the housing.

10. Replace the contact fluid after 24 hours at the latest.
11. Do not use cleaning solutions, vinegar, hot or even boiling water, etc. to clean the housing, contact fluid chamber, quartz or sensors.
12. Do not use alkaline aqueous-based cleaning solutions, aromatic hydrocarbons, ammonia or amines to clean the autoclavable plastic parts. Instead, use cleaners based on aliphatically saturated hydrocarbons, alcohol, diluted mineral acids, neutral or acidic saline solutions.

NOTE

The device may heat up on the underside in the case of extended use.

3.0 Intended use

Your **OPTINEB®-ir** ultrasonic nebulizer is a portable device that is intended to produce aerosols in various particle sizes by using different baffle plates (see Section 3.2). This ensures an optimal and identifiable deposition of your medication.

3.1 Function during ventilation

The **OPTINEB®-ir** ultrasonic nebulizer can be used with all ventilators.

It is only permissible to install the **OPTINEB®-ir** ultrasonic nebulizer into your ventilation system as specified in the operating instructions.

If the **OPTINEB®-ir** ultrasonic nebulizer is in operation, aerosol production takes place.

The fog generated is transported by the inspiratory flow to the patient, or is introduced via a T-piece by means of the control through the line for medication nebulization only during the inspiration phase directly at the tube body. (see sections 5.09/5.10/5.11)

3.2 Aerosol spectrum (particle size)

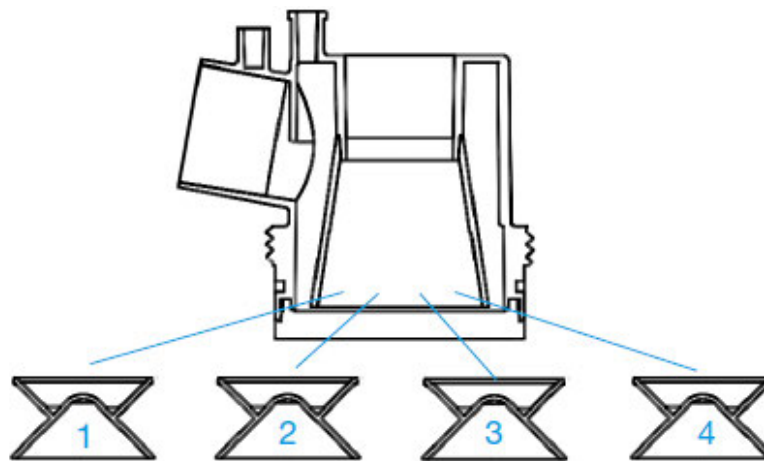
The particle size (MMAD/mass median aerodynamic diameter in μm) of the aerosol can be determined by using different baffle plates.

Baffle plate 1 (ON-117G) green color MMAD 2.3 μm alveolar deposition

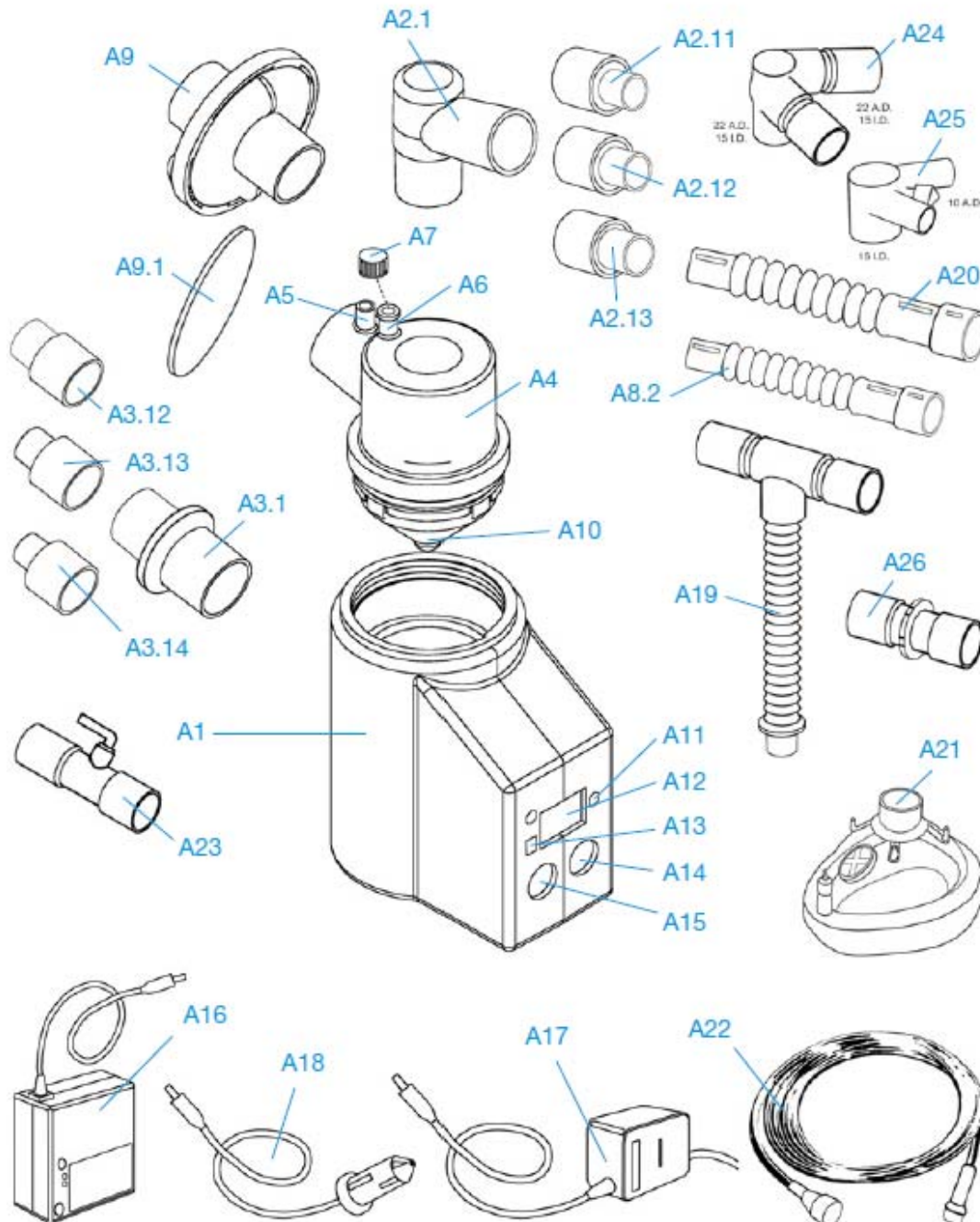
Baffle plate 2 (ON-117B) blue color MMAD 3.2 μm alveolar deposition

Baffle plate 3 (ON-117R) red color MMAD 3.8 μm bronchial deposition

Baffle plate 4 (ON-117Y) yellow color MMAD 4.5 μm tracheal deposition



4.0 The most important component parts of your OPTINEB®-ir ultrasonic nebulizer

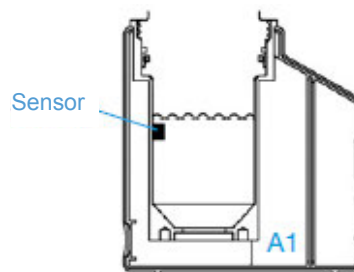


- A1** OPTINEB®-ir ultrasonic nebulizer (Item ON-100/2 – 2.4 MHz)
- A2.1** Angle adapter for respirator 22ID/22AD (Item ON-B-114)
- A2.11** Adapter 22AD 9-11 mmAD (Item ON-B-112)
- A2.12** Adapter 22AD 9-13 mmAD (Item ON-B-113)
- A2.13** Adapter 22AD 15AD (Item ON-B-121)
- A3.1** Adapter for respirator (Item ON-B-115)
- A3.12** Adapter 22ID 9-11 mmAD (Item ON-B-110)
- A3.13** Adapter 22ID 9-13 mmAD (Item ON-B-111)
- A3.14** Adapter 22ID 15AD (Item ON-B-122)
- A4** Nebuliser upper part (Item ON-103) with sealing ring (Item ON-110), baffle plate (Item ON-117B/G/R/Y) and screw cap by Luer/Lock (Item ON-116)
- A5** parking space for Luer/Lock screw cap
- A6** Luer/Lock connection
- A7** Luer/Lock screw cap (Item ON-116)
- A8.2** Kinder silicon hose 10.5 cm (Item ON-B-108)
- A9** Inhalation filter housing with valve and filter membrane (Item ON-101)
- A9.1** Filter membrane (Item ON-109)
- A10** Medication cup (Item ON-102)
Sterile medication cup (Item ON-102S)
- A11** Multifunction lamp
- A12** Display screen
- A13** Infrared sensor
- A14** On/Off switch
- A15** Start/Stop switch
- A16** Battery (Item ON-100A/ON-100HPA)
- A17** Power supply 110/230 VAC (Item ON-100N)
- A18** 12 V motor vehicle cigarette lighter adapter (Item ON-100Z)
- A19** Aerosol inlet hose system close to patient (Item ON-B-199)
- A20** Extension hose 22AD/15ID (Item ON-B-123)
- A21** Children's mask with exhalation valve size 1/2/3 (Item ON-122/123/124)
- A22** Luer/Lock hose for oxygen or control line for mechanical nebulization (Item ON-111)
- A23** Adapter for inspiratory flow (Item ON-B-119)
- A24** Adult Y-piece 22AD/14ID 22AD 22AD (Item ON-B-198)
- A25** Neonatal Y-piece 22AD/15ID 9-11 mm AD (Item ON-B-197)
- A26** Adapter for mask adaption 22 AD/22AD - 15 ID (Item ON-119)

5.0 Initial operation of your OPTINEB®-ir ultrasonic nebulizer for ventilation

Preparing the ultrasonic nebuliser.

- 5.01** Ensure first that the **OPTINEB®-ir [A1]** ultrasonic nebulizer is not connected to a power source. Remove any power supply by pulling out the connection cables from the socket. (Reverse side of **OPTINEB®-ir**).

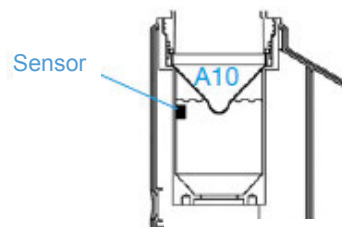


- 5.02** Take the **OPTINEB®-ir** ultrasonic nebulizer and fill it with 45 ml of **distilled or demineralized** water.

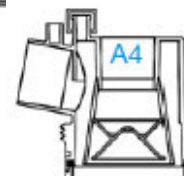
ATTENTION

The use of other contact fluids (e.g. tap water, sterile water or saline solution) is strictly prohibited since this can lead to significant impairment of the performance of the device and even to complete malfunction.

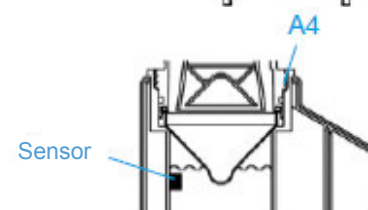
- 5.03** Insert a sterile medication cup [**A10**] with the tip facing downwards into the ultrasonic nebulizer. Bear in mind that the medication cup must be submerged in the contact fluid.



- 5.04** Now begin to assemble the autoclaved and therefore sterile plastic pieces. Begin with the top piece [**A4**]. Check whether the baffle plate is firmly seated in the housing, the sealing ring is in its guide and the white Luer/Lock plug is securely locked.

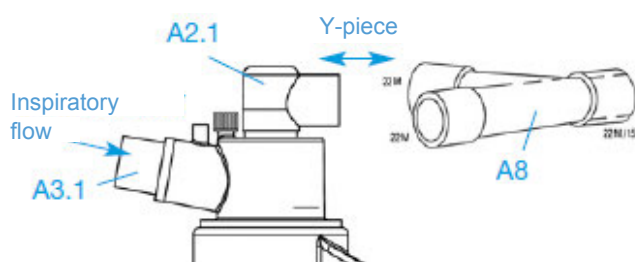


- 5.05** Now place the top piece [**A4**] on the ultrasonic nebulizer and turn it once on its own axis until a light click can be heard. Do not force when turning it.



Now the sterile medication cup that was inserted in Step 5.02 is firmly connected with the top piece and the ultrasonic nebulizer to form a closed system.

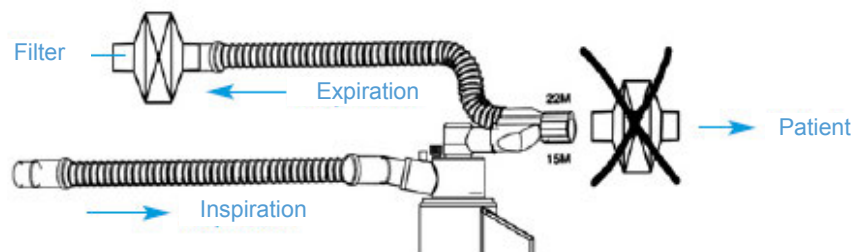
- 5.06** Now adapt the angle piece for ventilation [A2.1] with the upper opening of the top piece.
- 5.07** Now insert the adapter for ventilation [A3.1] into the opening outgoing to the side of the top piece using light pressure.
- 5.08** Now connect the Y-adapter [A8] onto the angle piece for ventilation [A2.1].



5.09 Use of OPTINEB®-ir in the inspiration branch of the ventilation system

Can be used with all ventilators.

Now integrate the **OPTINEB®-ir** ultrasonic nebulizer into the inspiration branch of your ventilation system. To do this, connect the inspiration hose with the blue adapter for ventilation on the **OPTINEB®-ir**. Orient the outlet of the angle piece toward the patient, and connect with a Y-piece. This is then adapted to an elbow or with the tube. Orient the still free outlet of the Y-piece (away from the patient), and connect with the expiration hose.



5.10 Use of OPTINEB®-ir in the ventilation system with climate-control filter

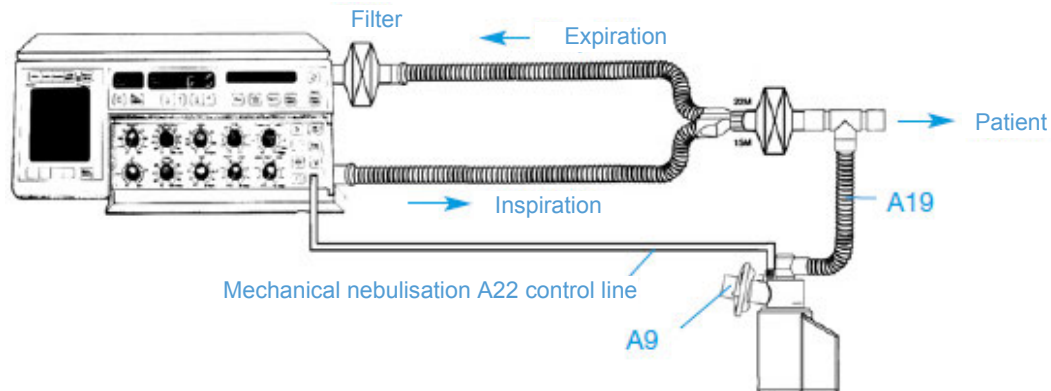
Can only be used with ventilators with the medication nebulization option.

If you are using climate-control filters or an active humidification for your ventilation, please proceed as specified below.

Insert the filter housing [A17] including an inserted filter membrane [A9.1] into the top piece [A4] on the side.

Unscrew the white Luer/Lock plug [A7] and place it on the parking space intended for it [A5]. Connect the control line for mechanical nebulization [A22] with the adapter of your ventilator intended for this purpose and with the Luer/Lock/connection [A6] of the **OPTINEB®-ir** ultrasonic nebulizer.

Now connect the **OPTINEB®-ir** [A1] ultrasonic nebulizer by adaption with the hose system for the aerosol inlet close to the patient [A19] with the ventilator hose system (T-piece between climate-control filter and tube).



(sterile hose system incl. control line, angle piece, 60cm creased tube and T-piece) [A19].

5.11 Use of OPTINEB®-ir in the ventilation system with coaxial hoses

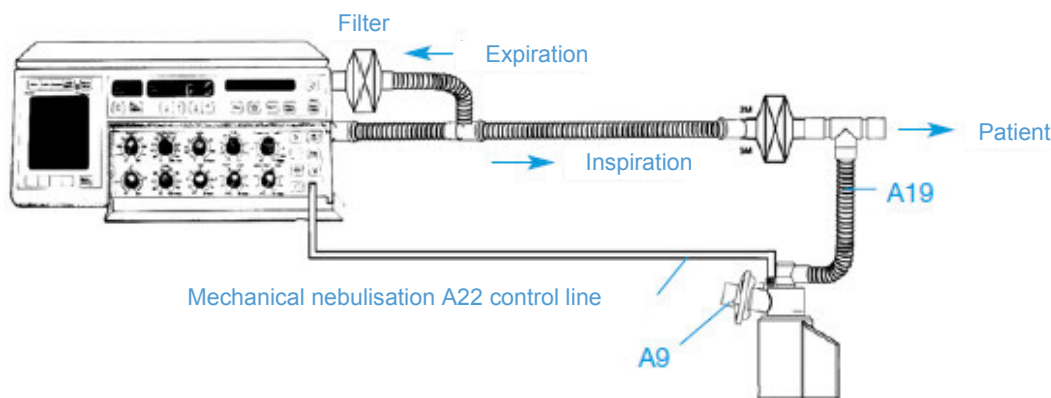
Can be used with ventilators with the medication nebulization option. If you are using coaxial hoses for your ventilation, please proceed as specified below.

Insert the filter housing [A9] including an inserted filter membrane [A9.1] into the top piece [A4] on the side.

Unscrew the white Luer/Lock plug [A7] place it on the parking space intended for it [A5]. Connect the control line for mechanical nebulization [A22] to the adapter of your ventilator intended for this purpose and with the Luer/Lock/connection of the **OPTINEB®-ir** ultrasonic nebulizer.

A climate-control filter can be used at the inspiratory end of the coaxial hose in the direction of the patient.

Now connect the **OPTINEB®-ir** [A1] ultrasonic nebulizer by adaption with the hose system for the aerosol inlet close to the patient [A19] with the ventilator hose system (T-piece between climate-control filter and tube).



(sterile hose system incl. control line, angle piece, 60cm creased tube and T-piece) [A19].

IMPORTANT

Use only sterile medication cups [A10] for use in the ventilator.

When using the **OPTINEB®-ir** in the ventilation system, use only sterile accessories.

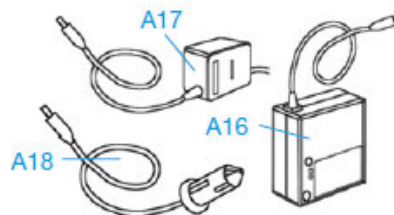
Aerosols only come into contact with the autoclaved parts and not with the actual device.

In order to protect your circle part from aerosol residue and your ventilator against damage, an end expiratory mechanical filter must be used (manufacturing company: Hudson, Pall, B+P, Tyco).

Compatibility checks are available for the most widely-used ventilators.

6.0 Power supply of the ultrasonic nebulizer OPTINEB®-ir.

The ultrasonic nebulizer can be operated with three different types of power source:
Alternating current 110/230 VAC, direct current 12 VDC (motor vehicles), or by battery.



6.1 Alternating current operation

Connect the AC power supply [A17] to the device, and plug the other end into the power outlet (110 or 220/230 Volt).

NOTE for alternating current operation

Do not use the device while bathing.
The device is to be set up so that it cannot fall into water.
Do not immerse the device into water or any other fluid.
Do not use the device if it has fallen into water.
Immediately pull out the mains plug.

6.2 Direct current outlet

Connect the car adapter [A18] to the device, and plug the other end into the corresponding 12V-DC socket (cigarette lighter in motor vehicle, etc.).

NOTE for direct current operation

Do not use the device while bathing.
The device is to be set up so that it cannot fall into water.
Do not immerse the device into water or any other fluid.
Do not use the device if it has fallen into water.
Immediately pull out the plug from the car adapter.

6.3 Battery operation

Nickel-cadmium battery [A16] or
Nickel-metal hybrid battery [A16]

- 6.3.1 The battery is charged through the power supply [A17]. For this, connect the plug of the power supply to the battery [A16]).
- 6.3.2 The charging time for the battery is approx. 8–10 hours.
- 6.3.3 Charging should never exceed 12 hours.
- 6.3.4 Battery operation is not possible while the battery is charging.
- 6.3.5 The battery must be disconnected from the power supply of the **OPTINEB®-ir** after charging.
- 6.3.6 Connect the charged battery only for the duration of the inhalation with the **OPTINEB®-ir**.
- 6.3.7 Please pull out the battery plug from the device after ending inhalation.
- 6.3.8 Only after the display [A12] of the **OPTINEB®-ir** shows the letter combination (LB) may the battery be charged again.



When the battery charge is 100%, operation of the ultrasonic nebulizer **OPTINEB®-ir** of approx. 40 min. is possible.

NOTE during battery operation

Do not use the device while bathing.
The device is to be set up so that it cannot fall into water.
Do not immerse the device into water or any other fluid.
Do not use the device if it has fallen into water.
Immediately pull out the battery plug.

CAUTION

In order to prevent damage to the ultrasonic nebulizer and ensure adherence to EMC guidelines, only the original power supply [A17] may be used.

NOTE

Drop off defective battery cells for disposal at battery disposal sites or return them to NEBU-TEC GmbH.

7.0 The meaning of the key assignment and the display screen of the OPTINEB®-ir ultrasonic nebulizer

When connecting the **OPTINEB®-ir** to the power supply, the last used or pre-set inhalation or nebulization program appears on the display [A12] whereby each program is briefly (for approx. 1 second) illuminated.

7.0.1 To switch on the nebulizer, press the “**On/Off**” [A14] sensor key (multifunction lamp [A17] lights up yellow).

7.0.2 To start aerosol production, press the “**Start/Stop**” [A15] key, nebulization starts (multifunction lamp lights up green).

7.0.3 In order to interrupt operation, please press the “**Start/Stop**” [A15] key during the nebulization process. Aerosol production is stopped (multifunction lamp lights up yellow) and PA (pause) appears on the display.

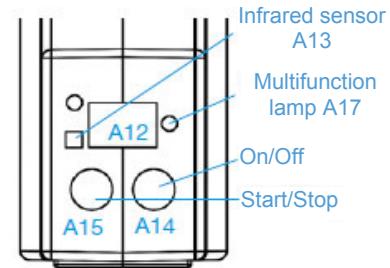
In order to restart nebulization, press the “**Start/Stop**” key [A15] again.

The display changes from “PA” in the time mode, the multifunction lamp lights up green and nebulization is continued.

Operation is ended when “En” (End) appears on the display. At the same time, an acoustic signal sounds when the device is switched off.

The length of the nebulization time (output per minute) can be influenced by the respective nebulization program or the ventilation parameters set.

7.0.4 After the end of inhalation, switch the device off “**On/Off**” [A14]



NOTE

The device is equipped with a multifunction lamp that displays the operation status:

Multifunction lamp:

Yellow light	-	Device ready for operation
Green light	-	Device in operation
Red light	-	Malfunction

Display indications [A12]



(LB) Empty battery



(LH) Contact fluid missing/incorrect contact fluid poured in



(SA) Contaminants or saline fluid poured in
(tap water, saline solution, mineral water, etc.)



(PA) Pause



(En) End

8.0 Program selection and operation of the OPTINEB®-ir ultra-sonic nebulizer for ventilation

With **OPTINEB®-ir**, 6 function programs are available:

- P 1 Not suitable
- P 2 Not suitable
- P 3 Volume-controlled inhalation with increasing output.
- P 4 Volume-controlled inhalation with constant output.
- P 5 Not suitable
- P 6 Intermittent operating mode, auto mode: Active/Passive operation, volume-controlled mode.

8.1 Programming mode only for authorized persons.

1. Proceed as follows to change the program:
2. Hold down both the “On/Off” and “Start/Stop” sensor keys.
3. Hold down both keys and connect **OPTINEB®-ir** with the power source.
4. Wait until the display starts to blink.
5. Then release both keys. The previously set program is indicated.
6. Move program selection down with the left key and up with the right key.
7. Approx. 7 sec. after the last key confirmation, the displayed program is saved.

8.2 Description of the ultrasonic nebulizer OPTINEB®-ir 2.4 MHz program

The following statements apply for programs P1 to P5:

- The main function of the keys “**Start/Stop**” and “**On/Off**” are identical.
- In program 6 (P6), the “**Start/Stop**” key is neutralized.
- The selection of the program is described in Point “8.1 Programming mode only for authorized persons”

8.2.1 Features of the first program (P1)

Program 1 was developed for the nebulization of special medications.

Non-adjustable nebulization time: max. 12 minutes. Time indication on the display runs from “0” going forward until the pre-set time is reached. The aerosol is intermittently generated (no continuous aerosol production). After expiry of the pre-set time, the program is ended.

8.2.2 Features of the second program (P2)

Program 2 was developed for the nebulization of special medications.

Non-adjustable nebulization time: max. 12 minutes.

Time indication on the display runs from “0” going forward until the pre-set time is reached. The aerosol is intermittently generated (no continuous aerosol production). After expiry of the pre-set time, the program is ended. The user is not able to change the program parameters.

8.2.3 Features of the third program (P3)

No fixed nebulization time. The device is volume-controlled (remaining quantity recognition) and produces aerosol until the medication has been nebulized. The **OPTINEB®-ir** ultrasonic nebulizer switches off automatically after reaching a remaining quantity of approx. 0.5 ml. The inhalation time may differ in length and results from the set ventilation parameters, the respiratory rate and the depth of respiration

The **OPTINEB®-ir** initially generates aerosol intermittently in order to prevent surge effects and then works continuously. The intermittent period is pre-set to 2 minutes. The user is not able to change the program parameters. In order to interrupt aerosol production, please press the “**Start/Stop**” [A15] key. By again pressing the “**Start/Stop**” [A15] key, you can re-activate aerosol production.

ATTENTION

Please note the maximum fill level of the medication to be nebulized. This may not be greater than 7.5 ml to ensure continuous aerosol production.

8.2.4 Features of the fourth program (P4)

Corresponds to Program P3 but without the initial intermittent time period. The user is not able to change the program parameters.

8.2.5 Features of the fifth program (P5)

Program P5 corresponds to the **OPTINEB** in the conventional version with the following features:

- Flexibly adjustable inhalation time. Preference settings 1 to 15 minutes.
- After expiry of the set time, the program is ended.
- The user can re-program the inhalation time within the pre-set range (see instruction manual for patients).

Setting the inhalation time (timer setting)

Simultaneously press both sensor keys:	Display flashes
Press the left “ Start/Stop ” [A15] key:	Adjust value down.
Press the right “ On/Off ” [A14] key:	Adjust value up.

8.2.6 Features of the sixth program (P6)

The program was designed for ventilation purposes. The active output intervals and the pause times are adjustable using the keypad. (See Point 8.3 Individual programming of Program 6 with the **OPTINEB®-ir**)

8.3 Individual programming of Program 6 with the **OPTINEB®-ir**

In order to program Program 6 in an individually customized way, please proceed as follows:

Select Program 6 as described in Point 8.1.

If you have selected Program 6, hold down both the ("**Start/Stop**" and the "**On/Off**") key simultaneously for approx. 2 seconds until the display flashes.

The number now flashing indicates the operation duration in seconds for the active phase (nebulization phase). Set the desired time by navigating with the ("**Start/Stop**" and "**On/Off**") keys. Once the desired time has been set, let the **OPTINEB®-ir** stand for approx. 5 seconds without pressing any keys. Then the set time will be automatically saved. Now the active phase is set.

In order to now set the passive phase, please perform the same steps.

Hold down both the ("**Start/Stop**" and the "**On/Off**") key simultaneously for approx. 2 seconds until the display flashes. Now you will see the previously set time of the active phase. Navigate with the "**On/Off**" key upwards until the number 15 appears. Press the "**On/Off**" key again and it shows "PA" in the display. Now you are in the parameter settings of the Pause phase. By further navigating with the "**On/Off**" key, you can also set the time of the Pause phase in seconds. Once the desired time has been set, let the **OPTINEB®-ir** stand for approx. 5 seconds without pressing any keys. Then the set time will be automatically saved.

Now the passive phase is set.

By pressing the "**Start/Stop**" key, the **OPTINEB®-ir** now starts to nebulize in the active/passive phase.

IMPORTANT

Please note the following details for custom programming of the sixth program:

The time of the active phase may not be greater/longer than the time of the passive phase, or the active phase of the nebulization may not be entered as greater than the time for the pause phase. When trying to adhere to this rule, the **OPTINEB®-ir** synchronizes the entries automatically to the value last entered.

Examples:

You first enter 8 seconds for the active phase and then 4 seconds for the passive phase. Now the **OPTINEB®-ir** synchronizes the active phase to 4 seconds, as the passive phase was the last to be set.

If you first set the passive phase to 8 seconds and then the active phase to 10 seconds, the **OPTINEB®-ir** synchronizes the passive phase to 10 seconds since the active phase was last set in this case.

IMPORTANT

Explanation using an additional example:

If you, for example, set the active phase to 10 seconds and the passive phase to 0, the seconds of the active phase are automatically converted to minutes – in this case 10 minutes. The **OPTINEB®-ir** then nebulizes for 10 minutes continuously.

In order to ensure the nebulization in an active/passive phase, two values must always be set (active/passive value).

Please also note the following:

The user of the device must ensure that the **OPTINEB®-ir** is connected as per our instruction manual.

The user of the device must adhere to the relevant recommendations of the manufacturer of the ventilation machine with regard to the administration of aerosols during ventilation.

NOTE

In program 6 (P6), the “**Start/Stop**” key is neutralized.

8.4 Volume-controlled mode

The device is volume-controlled (remaining quantity recognition) and produces aerosol until the medication has been nebulized.

The **OPTINEB®-ir** ultrasonic nebuliser switches off after reaching a remaining quantity of approx. 0.5 ml automatically. **En** (=End) appears in the display.



You can restart **OPTINEB®-ir** only after refilling approx. 2 ml of medication solution.

The nebulization time may differ in length and results from the set ventilation parameters.

NOTE

The remaining quantity left in the medication cup depends on the selected program:

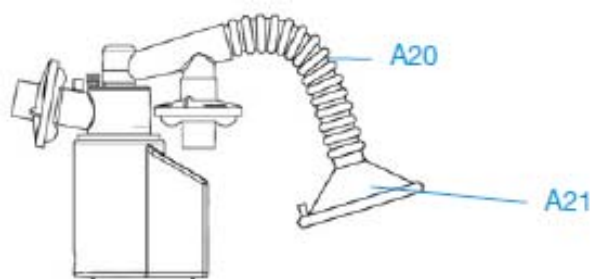
- P1 – approx. 0.5–1.5 ml remaining quantity
- P2 – approx. 0.5–1.5 ml remaining quantity
- P3/P4/P5/P6 – approx. 0.5 ml remaining quantity

ATTENTION

Please note the maximum fill level of the medication to be nebulized. This may not be greater than 7.5 ml to ensure continuous aerosol production.

9.0 Use of the **OPTINEB®-ir** ultrasonic nebulizer with a non-invasive ventilation mask.

Connect extension hose [A20] and mask [A21] with **OPTINEB®-ir**.



10.0 Cleaning instructions for OPTINEB®-ir

The **OPTINEB®-ir** ultrasonic nebulizer must be cleaned after use with one-time daily use or after the last inhalation in case of multiple daily inhalations. Cleaning must in general always be carried out when changing patients. By paying careful attention to the steps listed below, output can be maximized and the life of your ultrasonic nebulizer can be extended.

WARNING

Always disconnect the ultrasonic nebulizer from the power supply before cleaning.

Chemical resistance of the plastic used:

The plastic which we use has good resistance to saturated aliphatic hydrocarbons, alcohols, diluted mineral acids, and neutral and acidic saline solutions.

The plastic which we use is not resistant to aromatic hydrocarbons, ammonia, amines or alkaline aqueous solutions.

Temperature resistance of the plastic used:

The plastic which we use is temperature-resistant up to 134°C.

Sterilization procedure:

The following sterilization procedure can be applied with the plastic which we use:

- Ethylene oxide gas
- Superheated steam
- Hot air
- High-energy radiation (gamma and electron radiation)

10.1 Cleaning and replacement intervals of autoclaved plastic parts

Unscrew the nebulizer top piece (anti-clockwise) from the ultrasonic nebulizer. Remove the medication cup [A10] (disposable item). Please also unscrew the white Luer/Lock plug from the top piece (this plug cannot be autoclaved). Open the filter housing and remove the inserted filter membrane [A9.1] (disposable item). Now you can clean the plastic parts. Please note the aforementioned characteristics of the plastic (chemical resistance, temperature resistance, sterilization procedure).

IMPORTANT INFORMATION

Nebuliser top piece [A4] with sealing ring and baffle plate(s), exhalation part [A3], filter housing [A8/A9] and Luer/Lock screw cap [A7] should be replaced with multiple daily uses after 3 months. With one-time daily inhalation, the aforementioned items must be replaced according to wear and hygienic state.

10.2 Cleaning of the OPTINEB®-ir ultrasonic nebulizer.

WARNING:

Never immerse the housing of the ultrasonic nebulizer in water or in a cleaning solution.

Disconnect the power supply from the housing before cleaning the ultrasonic nebulizer.

Never subject the ultrasonic nebulizer to sterilization.

Shake the contact fluid out.

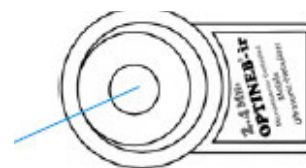
Flush the contact fluid reservoir with distilled water.

Place the ultrasonic nebulizer upside down on an absorbent pad and allow it to air dry in this position.

The ultrasonic oscillator (at the base of the water reservoir) should be carefully cleaned with a cotton bud 1-2 times per week (moving in a circular fashion).

Clean oscillator using cotton buds moving in a circular fashion.

USN view from above



CAUTION

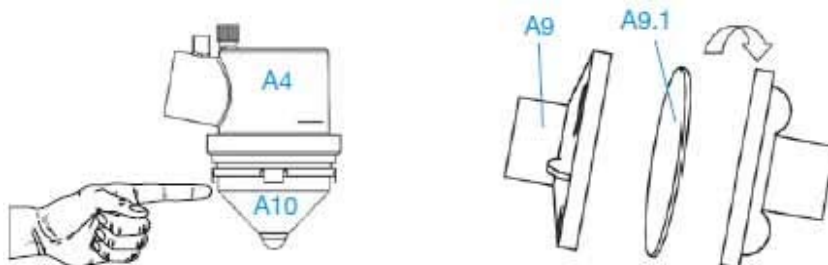
Never press too hard on the ultrasonic oscillator (at the base of the contact fluid reservoir). Non-observance can lead to damage.

Please wipe off the housing of the ultrasonic nebulizer using only a moist cloth or with a mild disinfection solution.

11.0 Replacement interval of medication cup and filter membrane

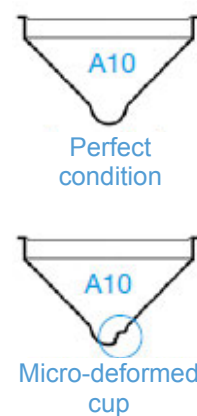
Medication cup, inhalation filter or filter membrane must be replaced when changing patients. All accessories coming into contact with the aerosol must also be replaced with sterile accessories. (top piece, baffle plate, adapter for ventilation and angle piece).

In-house hygiene instructions with regard to the replacement interval must be complied with as a matter of priority.



NOTE

The medication cups are disposable containers and must be replaced for hygiene and technical reasons daily (see Section 10.1). Non-adherence to the prescribed replacement intervals can lead to deformation of the medication cups [A10]. These micro-deformations of the medication cup [A10] can lower the output of the ultrasonic nebulizer considerably.



12.0 Servicing




The **OPTINEB®-ir ultrasonic nebulizer** should be serviced every 2 years. Servicing may only be performed by NEBU-TEC GmbH or a specifically authorized or qualified NEBU-TEC dealer.

WARNING

Do not open the housing. Non-observance results in the warranty being voided.

13.0 Information on trouble-shooting

If you believe that your USN is not properly functioning, please take the time to check or resolve possible defects before making a complaint about the device.

Symptoms	Possible causes	Trouble-shooting
Display indication  (LB/empty battery)	1. Power supply defect 2. Battery empty	1. Notify manufacturer or dealer 2. Charge battery
Display indication  (LH/no contact fluid)	1. No contact fluid in reservoir 2. Has been filled with sterile or purified water.	1. Fill with 45 ml of contact fluid (cover sensor) 2. Add approx. 1 ml tap water to the 45 ml of contact fluid.
Display indication  (SA/saline detection)	1. Has been filled with saline or contaminated liquid (e.g. tap water, salt, mineral water)	1. Carefully rinse several times with distilled water. Carefully clean the sensor in contact fluid reservoir with cotton buds or similar implement, rinse again with distilled water and then refill the contact fluid reservoir.

Lower Aerosol output (remaining quantity is too high)	<ol style="list-style-type: none"> 1. Used or damaged medication cup. 2. Contact fluid level in contact fluid reservoir too high/low. 3. Contact fluid reservoir not properly cleaned. 4. Several medication cups used. 	<ol style="list-style-type: none"> 1. Replace medication cup. 2. Fill contact fluid reservoir with 45 ml distilled water (use measuring cup with markings). 3. Clean device according to instructions. 4. Only use one medication cup.
Device doesn't generate any aerosol	<ol style="list-style-type: none"> 1. Several medication cups used. 2. Used or damaged medication cups used. 3. Device is not connected to power supply. 4. No contact fluid filled in contact fluid reservoir. 5. No fluid (medication solution) in the medication cup. 	<ol style="list-style-type: none"> 1. Only use one medication cup. 2. Use new medication cups. 3. Connect device to power supply. 4. Fill contact fluid reservoir up to the correct level. 5. Fill medication cup.
Inhalation or exhalation impeded	<ol style="list-style-type: none"> 1. Filter membrane is clogged or saturated. 2. Nebuliser top piece is not properly fastened. 	<ol style="list-style-type: none"> 1. Replace filter membrane. 2. Check if the nebulizer top piece is properly fastened.

14.0 Technical data of the OPTINEB®-ir ultrasonic nebulizer

Size	98 x 66 x 105 mm
Weight of basic device	280 g
Power supply type	Power supply unit 110/230 VAC
.....	12 V motor vehicle cigarette lighter adapter
.....	12 V battery
Electrical supply	12 VDC, 1.5 A maximum
Power consumption during operation	18 watt maximum
Ultrasonic frequency	2.4 MHz (nominal)
Nebuliser output	0.6 ml/min
MMAD	2.3/3.3/3.8/4.5 µm (depending on baffle plate)
Capacity of the medication cup	7.5 ml maximum
Capacity of the contact fluid reservoir	45 ml
Electrical protection class	II type B

15.0 Accessories

Item number	Description	Quantity
ON-100/2	OPTINEB®-ir 2.4 MHz	1
ON-100A	Battery for OPTINEB®-ir	1
ON-100HPA	High-performance battery for OPTINEB®-ir	1
ON-100N	Plug-in power supply 110–220 V	1
ON-100Z	12-V motor vehicle adapter	1
ON-113	Leather pouch for OPTINEB®-ir	1
ON-B-117	Stainless steel device holder for respirator	1
ON-B-202	Anesthesia support arm 30 cm long	1
.....	with device holder for OPTINEB®-ir stainless steel	
ON-B-203	Anesthesia support arm 50 cm long	1
.....	with device holder for OPTINEB®-ir stainless steel	
ON-B-204	Intensive support arm 100 cm long	1
.....	with device holder for OPTINEB®-ir stainless steel	
ON-B-205	Intensive support arm 120 cm long	1
.....	with device holder for OPTINEB®-ir stainless steel	

Non-autoclavable parts:

ON-102	Non-sterile medication cup	1
ON-102S	Sterile medication cup	1
ON-109	Filter membrane	1
ON-111	Oxygen hose with Luer/Lock	1
ON-B-199	Aerosol inlet hose system close to patient	1

ON-118	Measuring cup	1
ON-122	Special mask > Children – size 1 with expiratory valve Children /0–1 kg body weight	1
ON-123	Special mask > Children – size 2 with expiratory valve Children /1–8 kg body weight	1
ON-124	Mask > Children – size 3 with expiratory valve Children /8- kg body weight	1

Autoclavable parts:

ON-101	Filter housing with valve	1
ON-103	Top piece	1
ON-104	Exhalation piece	1
ON-105	Mouth piece	1
ON-110	Sealing ring	1
ON-117	Baffle plate blue – green – yellow – red	1
ON-B-108	Children's silicone hose 10.5 cm	1
ON-B-109	Adult's silicone hose 20.0 cm	1
ON-B-110	Neonatal adapter 22 ID / 9–11 mm	1
ON-B-111	Children's adapter 22 ID / 9–13 mm	1
ON-B-112	Neonatal adapter 22 AD / 9–11 mm	1
ON-B-113	Children's adapter 22 AD / 9–13 mm	1
ON-B-114	Angle piece for ventilation	1
ON-B-115	Adapter for ventilation	1
ON-B-119	Adapter for inspiratory flow	1
ON-B-120	Adapter for CO2 even measurement	1
ON-B-121	Children's adapter 22 AD / 15 AD	1
ON-B-122	Children's adapter 22 ID / 15 AD	1
ON-B-123	Elbow straight 22 AD / 15 ID swivel connector 15 AD smooth interior, 20 cm long	1
ON-B-197	Neonatal Y-piece 22 AD + 15 ID / 10 AD	1
ON-B-198	Adult Y-piece 22 AD + 15 ID / 22 AD	1

16.0 Compatibility

Compatibility explanation of LGA IC Bayern (Bavaria) is available.

17.0 Warranty

We provide you with a warranty of 24 months from the date of purchase for the **OPTINEB®-ir** ultrasonic nebulizer.

18.0 Declaration of conformity

Manufacturer: **NEBU-TEC** med. Product Eke Kern GmbH
Kreuzfeldring 17
63820 Elsenfeld - GERMANY

Phone: +49(0)6022-610 62-0
Fax: +49(0)6022-64 98 12
E-mail: nebu-tec@t-online.de
Web: <http://www.nebu-tec.de>

Product name: **OPTINEB®-ir**
Model/Type: ON-100/2-2.4 MHz

We herewith declare that the aforementioned product conforms to the requirements of the EC guideline 93/42/EEC.



Applicable standards:
Quality system standard **DIN EN ISO 9001**
Safety standard **DIN EN 60601-1**
EMC standards **DIN EN 60601-2**
EN 55011

19.0 Garantiekarte zum Abtrennen/Warranty Card (tear-off card)

Garantiekarte/Warranty Card

Typ/Type: VN-100/4-2,4 MHz

Geratenummer/Serial Number:

Kaufdatum/Purchase Date:

Benutzer, Handler/User, Dealer

Name:

Strasse, Adresse/Street, Address:

.....

PLZ, Ort/Zip Code, Town:

.....

Land/Country:

Stempel/Stamp:



I, William L. Chisholm, declare that:

1. I am fluent in both German and English. To the best of my knowledge and belief, the attached document is a true and correct translation of a user manual for OPTINEB®-ir from German to English.

2. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001.

Date:



NAME OF TRANSLATOR

EXHIBIT 27

VENTA-NEB®-ir A-I-C-I®

Microprocessor Controlled • Mobile Ultrasonic Nebulizer
for VENTAVIS® Inhalation

Mikroprozessor gesteuerter mobiler Ultraschallvernebler

Gebrauchsanweisung

Operating Instructions

für Heimtherapie/spontan atmende Patienten
for home therapy / spontaneously breathing patients



Gerätetyp/Unit Type

VN-100/4-2,4 MHz

Hergestellt in Deutschland/

Made in Germany

NEBU-TEC med. Produkte

Eike Kern GmbH

Kreuzfeldring 17

63820 Elsenfeld - GERMANY

Tel.: (+49) (0)6022-610 62 0

Fax: (+49) (0)6022-610 62 99

e-mail: nebu-tec@t-online.deweb: <http://www.nebu-tec.de>**VENTA-NEB®-ir A-I-C-I®**

Microprozessorgesteuerter mobiler Ultraschallvernebler

Gebrauchsanweisung

Gerätetyp: VN-100/4-2,4 MHz

Hergestellt in Deutschland

Sehr geehrte Patientin, sehr geehrter Patient,
mit dem mobilen Ultraschallvernebler **VENTA-NEB®-ir** haben Sie ein absolut präzise eingestelltes und im Klimaraum justiertes Inhalationsgerät erhalten. Um Ihnen eine konstante Funktion des Gerätes zu gewährleisten bitten wir Sie, die Gebrauchsanleitung aufmerksam zu lesen und den Anweisungen zu folgen, wenn Sie das Gerät in Betrieb nehmen.

Wir wünschen einen guten Behandlungserfolg beim Einsatz Ihres **VENTA-NEB®-ir**

**VENTA-NEB®-ir A-I-C-I®**

Microprocessor Controlled - Mobile Ultrasonic Nebulizer

Operating Instructions

Unit Type VN-100/4-2.4 MHz

Made in Germany

Dear Patient,
With the mobile Ultrasonic Nebulizer **VENTA-NEB®-ir** you received an inhalation device that was adjusted extremely precise in a conditioned room. In order to ensure a constant operation of the equipment we ask you to carefully read the operating manual and to follow the instructions before you put the device into service.
We wish you every success for your treatment with the **VENTA-NEB®-ir**.

Inhaltsverzeichnis

- 1.0 Bildzeichen
- 2.0 Sicherheitshinweise
- 3.0 Verwendungszweck
- 3.1 Erläuterungen zu Betriebsarten/Programmwahl
- 3.2 Funktion bei Spontanatmung/Heimtherapie
- 3.4 Aerosolspektrum (Partikelgröße)
- 4.0 Die wichtigsten Bestandteile Ihres Ultraschallverneblers
- 5.0 Inbetriebnahme Ihres Ultraschallverneblers über Mundstück
- 6.0 Stromversorgung des Ultraschallverneblers
- 7.0 Bedienung des Ultraschallverneblers
- 7.1 Programmierung und Einstellungen
- 7.1.1 **VENTA-NEB®-ir** 2,4 MHz
- 8.0 Einsatz eines Verlängerungsschlauchs bei Inhalation im Liegen
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- 9.0 Reinigung
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- 11.0 Wartung
- 12.0 Hinweise zur Fehlersuche
- 13.0 Technische Daten
- 14.0 Zubehör / Bestellinformationen **VENTA-NEB®-ir**
- 15.0 Garantie
- 16.0 Konformitätserklärung
- 17.0 **Garantiekarte zum Abtrennen**

1.0 Bildzeichen



Achtung, Gebrauchsanleitung einsehen



Gerät der Schutzklasse II



Anwendungsteil Typ B



Gerät der Klasse AP



2.0 Sicherheitshinweise

Jede Handhabung an dem Gerät setzt die genaue Kenntnis und Beachtung dieser Gebrauchsanweisung voraus. Die Haftung für die sichere Funktion des Gerätes geht auf jeden Fall an den Betreiber über, wenn ein Fremdeingriff erfolgt oder eine Handhabung, die nicht der bestimmungsgemäßen Verwendung entspricht. Wichtige Informationen werden durch folgende Ausdrücke hervorgehoben:

WARNUNG

Wichtige Sicherheitsinformation zu Gefahren, die zu Körperverletzungen führen können.

ACHTUNG

Wichtige Information zu Bedienungsschritten, die Fehlfunktionen des Gerätes verursachen können.

VORSICHT

Information, die Schäden am Produkt verhindert.

HINWEIS

Information, die Sie besonders beachten sollten.
[Bestandteile siehe Skizze 4.0]

Bitte lesen Sie die Gebrauchsanweisung vor der ersten Inbetriebnahme aufmerksam durch. Bewahren Sie die Gebrauchsanweisung sorgfältig auf.

WARNUNG

1. Den Netzstecker nach jedem Gebrauch ziehen.
2. Das Gerät nicht benutzen während Sie baden.
3. Das Gerät so aufstellen, dass es nicht in Wasser fallen kann.
4. Das Gerät nicht in Wasser oder andere Flüssigkeiten eintauchen.
4. Das Gerät nicht benutzen, wenn es in Wasser gefallen ist, sofort den Netzstecker ziehen.
6. Das Gerät nicht im Regen verwenden.
7. Das Gerät nicht in der Nähe von leicht entzündbaren Stoffen verwenden.
8. Nie Hände oder Finger in den Medikamentenbehälter stecken, während das Gerät in Betrieb ist.

ACHTUNG

1. Eingeschaltete HF-Kommunikationseinrichtungen (Funktelefone o.ä) in der Umgebung vom **VENTA-NEB®-ir**, können seine Funktion beeinflussen.
2. Ein elektrisches Gerät sollte nie unbeaufsichtigt betrieben werden.
3. Besondere Vorsicht ist geboten, wenn das Gerät von bzw. in der Nähe von Kindern oder Schwerkranken benutzt wird.
4. Das Gerät lediglich für die beabsichtigten, in dieser Gebrauchsanweisung aufgeführten Zwecke benutzen. Keinesfalls Zubehörteile einsetzen, die nicht vom Hersteller empfohlen sind.
5. Niemals dieses Gerät betreiben, wenn:
 - a) das Netzkabel oder der Stecker beschädigt ist.
 - b) das Gerät nicht ordnungsgemäß funktioniert.
 - c) das Gerät fallengelassen oder beschädigt wurde.
 - d) das Gerät in Wasser gefallen ist. In solchen Fällen das Gerät zwecks Überprüfung und Reparatur dem Hersteller oder einem anerkannten NEBU-TEC-Fachhändler übersenden.
6. Das Netzkabel von aufgeheizten Oberflächen fernhalten.
7. Das Gerät auf einer ebenen und stabilen Oberfläche so aufstellen, dass keine Luftöffnungen verschlossen werden.
8. Das Gerät nicht verwenden, während Sie schlafen.
9. Niemals Gegenstände in die Öffnungen des Gerätes stecken.
10. Den Ultraschallvernebler nie in der Spülmaschine, oder Mikrowelle reinigen. Basisgerät nie direkter Mikrowellenstrahlung aussetzen.

11. Bei der Reinigung der Kontaktflüssigkeitskammer ist zu vermeiden, dass Nässe von außen ins Gehäuse eindringen kann.
12. Kontaktflüssigkeit nach 24 Std. wechseln.
13. Keine Reinigungslösungen, Essigwasser, heißes od. gar kochendes Wasser, etc. zum Reinigen von **Gehäuse, Kontaktflüssigkeitskammer, Quarz oder Sensor** benutzen.
14. Keine Reinigungslösungen auf wässriger alkalischer Basis, aromatische Kohlenwasserstoffe, Ammoniak und Amine, zum Reinigen der **autoklavierbaren Kunststoffteile** benutzen. Verwenden Sie stattdessen Reiniger auf gesättigter aliphatischer Kohlenwasserstoffbasis, Alkohole, verdünnte Mineralsäuren, neutrale und saure Salzlösungen.

HINWEIS

Das Gerät **VENTA-NEB®-ir** unterliegt während der Inbetriebnahme keinen besonderen Maßnahmen hinsichtlich der elektromagnetischen Verträglichkeit. Gerät nicht zur Fremdnutzung verleihen.
Nur das von Ihrem Arzt verordnete Medikament inhalieren.
Das Gerät kann sich bei längerer Benutzung an der Unterseite erwärmen.

3.0 Verwendungszweck

Ihr **VENTA-NEB®-ir** Ultraschallvernebler ist ein tragbares Gerät, das dafür vorgesehen ist, Aerosole in konstanten Partikelgrößen zu produzieren (siehe 3.3.). Dies gewährleistet eine optimale Deposition des Medikamentes.

3.1 Erläuterung zu Betriebsarten/Programmwahl

Um dem Anwender eine Kontrolle über das eingestellte und aktivierte Programm zu ermöglichen, leuchtet nach dem Verbinden des Ultraschallverneblers mit dem Stromkreislauf das aktivierte Programm kurz (für ca. 1 Sekunde) im Display auf:
- **VENTA-NEB®-ir** 2,4 MHz: 2 Programme (P1 od. P2)

3.2 Funktion von A-I-C-I® bei Spontanatmung/Heimtherapie

A-I-C-I® (active intermitt controlled inhalation /Aktive intermittierende kontrollierte Inhalation)
Ist das Inhalationsgerät in Betrieb gibt das Gerät vor, wann und wie oft eingeatmet (inhaliert) wird.

Akustisches Signal:

Ausatmung

Akustisches und Optisches Signal(grüne Lampe [A11.1]): Einatmung

Durch dieses Inhalationsschema wird eine bessere Deposition und eine absolut genaue Dosierung des Medikamentes gewährleistet.

Der erzeugte Nebel kann über das Mundstück [A2] (oder Maske [A21]) inhaliert werden. Die Ausatmung erfolgt ebenso über das Mundstück oder die Maske und wird durch Ventile, die in dem (nicht vertauschbaren) Filtergehäuse [A8, A9] angebracht sind, gesteuert. Diese Filter verhindern jeglichen Aerosolaustritt in die Raumluft und bilden somit ein geschlossenes System der Verneblereinheit.

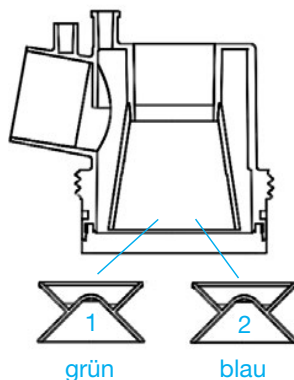
Am Oberteil [A4] des Gerätes befindet sich ein Luer/Lock-Anschluß [A6], über diesen Anschluß ist die Zugabe der Medikation möglich, ohne die Verneblereinheit zu öffnen.

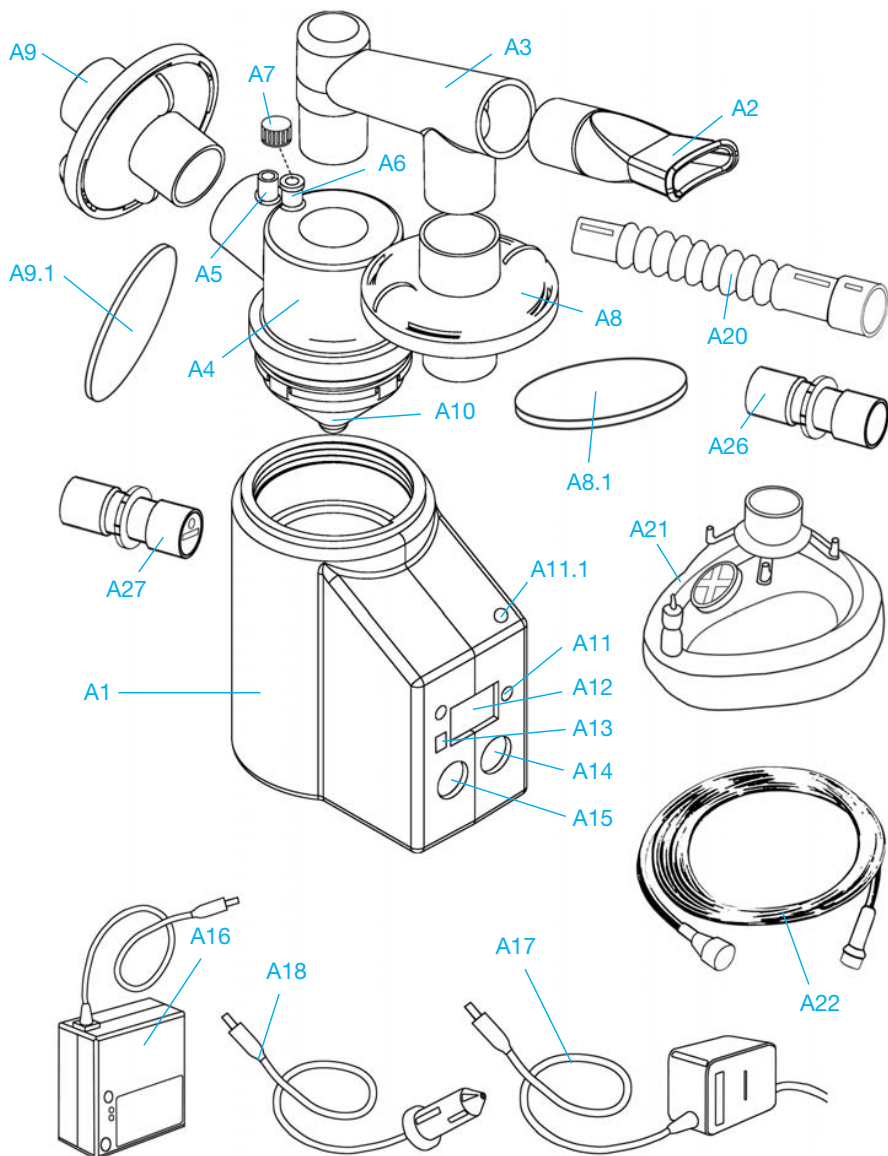
Gleichzeitig kann über diesen Anschluß Sauerstoff gegeben werden.

3.3 Aerosolspektrum (Partikelgröße)

Die Partikelgröße (MMAD/Mass Median Aerodynamic Diameter in μm) des Aerosols ist beim Einsatz der grünen Prallplatte und VENTAVIS® Lösung 2,3 μm ,
 der blauen Prallplatte und VENTAVIS® Lösung 3,2 μm .

Prallplatte 1 (VN-117G) Farbe Grün	MMAD 2,3 μm	mit VENTAVIS® gemessen
Prallplatte 1 (VN-117B) Farbe Blau	MMAD 3,2 μm	mit VENTAVIS® gemessen



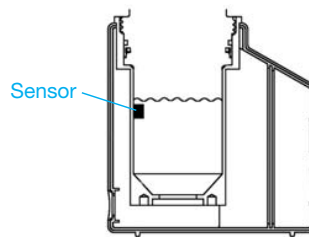
4.0 Die wichtigsten Bestandteile Ihres Ultraschallverneblers VENTA-NEB®-ir

- A1** VENTA-NEB®-ir Ultraschallvernebler
- A2** Mundstück (Art. VN-105)
- A3** Ausatemteil (Art. VN-104)
- A4** Vernebleroberteil (Art. VN-103) mit Dichtring (Art. VN-110), Prallplatte (Art. VN-117B/G/R/Y) und Verschlusskappe Luer/Lock (Art. VN-116)
- A5** Parkplatz für Luer/Lock Verschlusskappe
- A6** Luer/Lock Anschluß
- A7** Verschlusskappe Luer/Lock (Art. VN-116)
- A8** Ausatemfiltergehäuse mit Ventil (Art. VN-101)
- A8.1** Ausatemfiltermembrane (Art. VN-109)
- A9** Einatemfiltergehäuse mit Ventil (Art. VN-101)
- A9.1** Einatemfiltermembrane (Art. VN-109)
- A10** Medikamentenbecher (VN-102)
- A11** Multifunktionslampe
- A11.1** Lampe zur Inhalationsaufforderung
- A12** Anzeigendisplay
- A13** Infrarotsensor
- A14** Ein/Aus-Schalter
- A15** Start/Stop-Schalter
- A16** Akku (Art. VN-MCA)
- A17** Netzteil 11/230 VAC (Art. VN-100N)
- A18** 12 V KFZ-Adapter Zigarettenanzünder (Art. VN-100Z)
- A20** Verlängerungsschlauch 22AD/15ID (Art. VN-B-109)
- A21** Kinder-Maske mit Ausatemventil Größe 1/2/3 (Art. VN-122/123/124) Z
- A22** Schlauch Luer/Lock für O₂ od. Med. Verneblersteuerleitung (Art. VN-111)
- A26** Adapter für Maskenadaption 22 AD/22AD - 15 ID (Art. VN-119)
- A27** Inhalationstrainer

5.0 Inbetriebnahme Ihres Ultraschallverneblers (USV) VENTA-NEB®-ir bei Inhalation mit Mundstück

Vorbereiten des Ultraschallverneblers

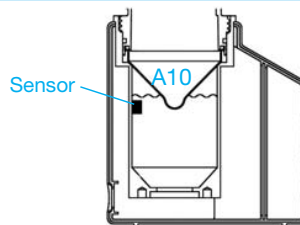
- 5.01** Den Netzstecker **[A17]** entfernen, um ein unbeabsichtigtes Einschalten des Verneblers zu vermeiden.
- 5.02** Den Kontaktflüssigkeitsbehälter mit destilliertem oder entmineralisiertem (demineralisiertem) Wasser bis zur blauen Markierung mittels Meßbecher befüllen. Der Sensor muss mit dieser Kontaktflüssigkeit bedeckt sein (ca. 45 ml).



ACHTUNG

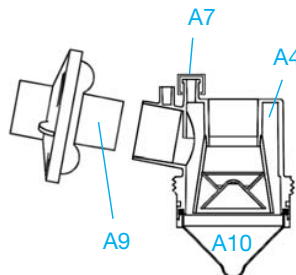
Die Verwendung von anderen Kontaktflüssigkeiten (wie z. B. Leitungswasser, steriles Wasser oder Kochsalzlösung) ist strengstens verboten, da dies zur wesentlichen Beeinträchtigung der Leistung des Gerätes bis hin zum totalen Ausfall führen kann.

- 5.03** Den Medikamentenbecher [A10] einsetzen.
Bitte achten Sie darauf, dass die Spitze des Medikamentenbechers in die Kontaktflüssigkeit eintaucht.

**HINWEIS**

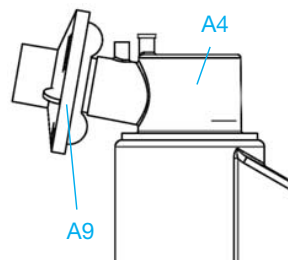
Der Medikamentenbecher [A10] ist ein Einwegartikel. Vor jedem Einsatz sollte dieser sorgfältig auf Schäden untersucht werden. Ist der Medikamentenbecher beschädigt oder ist die Medikamentenausgabe zu niedrig, so muss der Medikamentenbecher ausgewechselt bzw. der Ultraschallschwinger gereinigt werden.

- 5.04** Vergewissern Sie sich, dass die Prallplatte richtig im Vernebleroberteil [A4] befestigt, ein Dichtring eingelegt und die Luer/Lock Verschlusskappe [A7] mit dem Oberteil konnektiert ist.



- 5.05** Stecken Sie das Filtergehäuse [A9] mit der Einatemfiltermembran [A9.1] in die dafür vorgesehene Öffnung des Oberteils [A4].

- 5.06** Das Oberteil [A4] mit dem Einatemfilter [A9] zum hinteren Teil des Gerätes hin ausgerichtet aufsetzen und im Uhrzeigersinn solange drehen, bis ein deutliches Knacken zu hören ist. Dieses Geräusch wird durch die Verbindung des Medikamentenbechers [A10] mit dem Oberteil [A4] erzeugt.

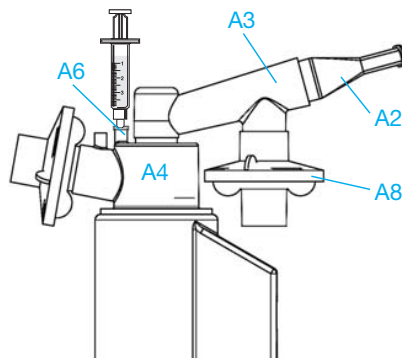


5.07 Das Mundstück [A2] das Ausatemteil [A3] und das Ausatemfiltergehäuse [A8] zusammensetzen und mit dem Oberteil [A4] verbinden.

5.08 Die Flüssigkeit (Medikamentenlösung), die inhaliert werden soll, durch die dafür vorgesehene Öffnung [A6] (Luer/Lock Anschluß) im Vernebleroberteil [A4] mit Hilfe einer Spritze einfüllen.

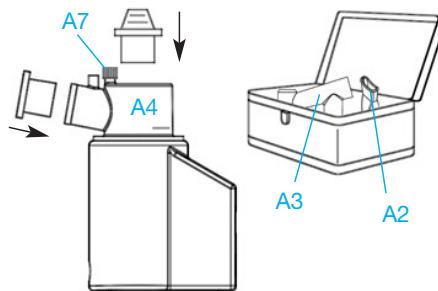
5.09 Den Luer/Lock Anschluß [A6] mit der Verschlusskappe [A7] verschließen.

5.10 Das Gerät wie unter Punkt 7.0 – 7.1 der Bedienungsanleitung beschrieben in Betrieb nehmen.



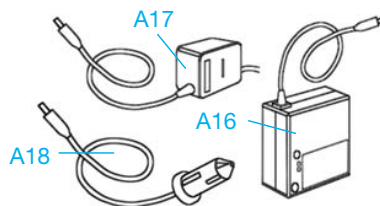
HINWEIS

Bei mehrmaliger täglicher Inhalation oder bei Transport zwischen den einzelnen Inhalationen sollte das Oberteil [A4] mit der beigefügten Luer/Lock Verschlusskappe [A7], sowie den beiden Verschußstopfen aus hygienischen Gründen verschlossen werden. Das Mundstück [A2], Ausatemteil [A3] und die beiden Filtergehäuse [A8,A9] sind dann in der Safetybox aufzubewahren.



6.0 Stromversorgung des Ultraschallverneblers VENTA-NEB®-ir

Der Ultraschallvernebler kann mit drei verschiedenen Stromquellen betrieben werden: Wechselstrom-110/230 VAC, Gleichstrom-12 VDC (KFZ) oder mit Akku.



6.1 Wechselstrombetrieb

Das AC-Netzteil [A17] an das Gerät anschließen und das andere Ende in die Steckdose stecken (110 od. 220/230 Volt).

HINWEIS bei Wechselstrombetrieb

Das Gerät nicht benutzen während Sie baden.

Das Gerät so aufstellen, dass es nicht in Wasser fallen kann.

Das Gerät nicht in Wasser oder andere Flüssigkeiten eintauchen.

Das Gerät nicht benutzen, wenn es in Wasser gefallen ist. Sofort den Netzstecker ziehen.

6.2 Gleichstrombetrieb

Den Kfz-Adapter [A18] an das Gerät anschließen und das andere Ende in den Zigarettenanzünder stecken.

HINWEIS bei Gleichstrombetrieb

Das Gerät nicht benutzen während Sie baden.

Das Gerät so aufstellen, dass es nicht in Wasser fallen kann.

Das Gerät nicht in Wasser oder andere Flüssigkeiten eintauchen.

Das Gerät nicht benutzen, wenn es in Wasser gefallen ist.

Sofort den Stecker des Kfz-Adapters ziehen.

6.3 Akkubetrieb

Bitte separate Bedienungsanleitung beachten

6.3.1 Ladevorgang nur mit dem Originalnetzteil [A17] durchführen.

Verbinden Sie dazu den Stecker des Netzteils mit dem Akku [A16]

6.3.2 Die Ladezeit für den Akku beträgt, je nach Ladezustand, bis zu 12 Stunden.

6.3.3 Während des Ladevorgangs ist der Betrieb des Akkus nicht möglich.

6.3.4 Wenn der Aufladevorgang beendet ist, erscheint im Display nacheinander die Buchstabenkombination „E“, „n“, „d“ (= Ende). Der Akku ist nun betriebsbereit.

6.3.5 Falls Sie den Akku nicht sofort einsetzen möchten, darf dieser, auch trotz des abgeschlossenen Ladevorganges, für längere Zeit (mehrere Tage) am Netzteil bleiben.

6.3.6 Den aufgeladenen Akku nur für die Dauer der Inhalation mit dem **VENTA-NEB®-ir** verbinden.

6.3.7 Bitte entfernen Sie den Stecker des Akkus nach beenden der Inhalation vom Gerät.

6.3.8 Zum Anzeigen der Akkuladung halten Sie bitte die Taste für die Ladestandsanzeige ca. 3 sec. gedrückt. Im Display erscheint die Akkukapazität in %.



Bei 100% Akkuladung ist ein Betrieb des Ultraschallverneblers **VENTA-NEB®-ir** von ca. 2 Wochen möglich.

HINWEIS bei Akkubetrieb

Das Gerät nicht benutzen während Sie baden.

Das Gerät so aufstellen, dass es nicht in Wasser fallen kann.

Das Gerät nicht in Wasser oder andere Flüssigkeiten eintauchen.

Das Gerät nicht benutzen, wenn es in Wasser gefallen ist.

Sofort den Stecker des Akkus ziehen.

VORSICHT

Um eine Beschädigung des Ultraschallverneblers zu vermeiden und um die Einhaltung der EMV EN 55011 Richtlinien zu gewährleisten, darf nur das Original-Netzteil **[A17]** oder der Original-Akkupack **[A16]** eingesetzt werden.

HINWEIS

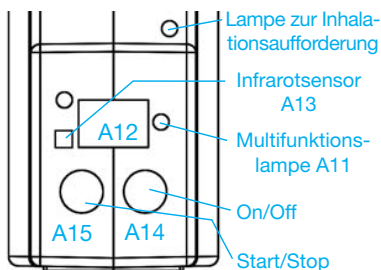
Defekte Akku-Batteriezellen zur Entsorgung in Batterieentsorgungsstellen abgeben, oder an NEBU-TEC GmbH zurückschicken.

7.0 Bedienung des Ultraschallverneblers VENTA-NEB®-ir

Beim Anschließen des **VENTA-NEB®-ir** an das Stromnetz erscheint das von Ihrem Arzt eingestellte Inhalationsprogramm im Display **[A12]**, indem das jew. Programm kurz (für ca. 1 Sekunde) aufleuchtet.

7.01 Zum Einschalten des Verneblers die Sensortaste **On/Off** drücken die Multifunktionslampe **[A11]** leuchtet gelb. In der Anzeige wird die Anzahl der Inspirationszyklen gezeigt.

7.02 Zum Starten der Inhalation die Taste **Start/Stop [A15]** drücken (ein Akustisches Signal ist zu hören) dabei langsam ausatmen. Beim nächsten akustischen Signal mit gleichzeitigem optischen Signal **[A11.1]** (grüne Lampe leuchtet) langsam und gleichmäßig einatmen. Nach dem Einatmen kurz die Luft anhalten dann langsam ausatmen. (Um richtiges Inhalieren zu erlernen und die Inhalation zu optimieren sollten Sie den Inhalationstrainer **[A27]** benutzen). Den Inhalationstrainer mit dem Einatemfilter konnektieren.



7.03 Um die Aerosolproduktion zu unterbrechen, betätigen Sie bitte die Taste **Start/Stop [A15]**. Die Multifunktionslampe **[A17]** leuchtet gelb auf und PA (Pause) erscheint auf dem Display **[A12]**.

Um die Aerosolproduktion fortzusetzen, betätigen Sie erneut die Taste **Start/Stop [A15]**.

Die Anzeige wechselt von PA in den Zeitmodus, die Multifunktionslampe leuchtet grün auf, die Verneblung wird fortgesetzt.

Die Inhalation ist dann beendet, wenn im Display En (Ende) erscheint. Gleichzeitig ertönt ein akustisches Signal am Ende der Inhalation.

7.04 Das Mundstück **[A2]** mit den Lippen umschließen und das Aerosol über den Einatemfilter und das Ventil inhalieren, indem Sie langsam und tief einatmen. Die Ausatmung erfolgt ebenfalls über das Mundstück und den Ausatemfilter mit Ventil.

Die Inhalationsanleitung: 'Wie inhaliere ich richtig', ist separat erhältlich.

7.05 Inhalieren Sie so lange, bis das jeweilige Verneblungsprogramm abgelaufen ist. Dies wird durch ein akustisches Signal und En (Ende) im Display signalisiert. Die Länge der Inhalation kann vom jeweiligen Verneblerprogramm abhängig sein.

7.06 Nach Beendigung der Inhalation das Gerät ausschalten (**On/Off**) **[A14]** und den Ultraschallvernebler von der jeweiligen Stromversorgungsquelle trennen.

HINWEIS

Das Gerät ist mit einer Multifunktionslampe (A11] und einer Lampe zur Inhalationsaufforderung [A11.1] ausgerüstet.

Lampe zur Inhalationsaufforderung [A11.1]

Grünes Licht leuchtet - Inhalation beginnt.
Grünes Licht aus - Inhalation zu Ende bzw. Pause.

Multifunktionslampe [A11]:

Gelbes Licht - Gerät betriebsbereit
Grünes Licht - Gerät in Betrieb
Rotes Licht - Störung

Displayanzeigen [A12]



(LB) Leere Batterie



(LH) Kontaktflüssigkeit fehlt/falsche Kontaktflüssigkeit
eingefüllt



(SA) Verunreinigte od. salzhaltige Flüssigkeit eingefüllt
(Leitungswasser, Kochsalz, Mineralwasser, etc...)



(PA) Pause



(En) Ende

HINWEIS

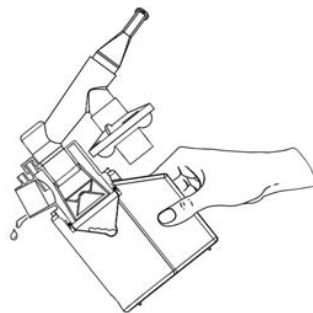
Der Wirkstoffanteil Ihres Medikamentes in der verbleibenden Restmenge ist gering, und somit nicht für eine neue Inhalation zu verwenden.

Zur Überprüfung der Restmenge kann das Gerät auf den Kopf gestellt und die Restmenge über die Skalierung im Oberteil [A4] abgelesen werden.
Das Gerät ist bis 7,5 ml Flüssigkeit im Medikamentenbecher auslaufsicher.

HINWEIS

Die Restmenge der im Medikamentenbecher verbliebenen Medikation muss nach jeder Inhalation ausgeschüttet werden.

Zum Ausschütten der Restmenge den Einatemfilter [A9] entfernen und das restliche Medikament durch Kippen des Gerätes ausschütten



7.1 Programmierung und Einstellungen des Ultraschallverneblers

Die Auswahl des Verneblungsprogrammes wird vom behandelnden Arzt sowie von dem dazu befugten technischen Personal anhand der Empfehlung des Arztes vorgenommen. Der Hersteller des **VENTA-NEB®-ir** gibt keine Dosierungsempfehlungen für Medikamente. Bei der inhalativen Anwendung beachten Sie bitte jeweils den Beipackzettel des Medikamentes.

7.1.1 Programmierung und Einstellungen des VENTA-NEB®-ir 2,4 MHz

Der Ultraschallvernebler **VENTA-NEB®-ir 2,4 MHz** ermöglicht es dem Patienten, zwischen 2 verschiedenen Verneblungsprogrammen auszuwählen.

Beim Anschluß des **VENTA-NEB®-ir 2,4 MHz** an das Stromnetz wird das jeweilig eingestellte Verneblungsprogramm kurz (ca. 1 Sekunde) im Display angezeigt.

P1	Programm 1	5,0 µg Wirkstoff am Mundstück	25 Inhalationszyklen
P2	Programm 2	2,5 µg Wirkstoff am Mundstück	10 Inhalationszyklen

Wechsel des Verneblungsprogrammes beim VENTA-NEB®-ir 2,4 MHz

Zum Wechseln der Programme beim **VENTA-NEB®-ir 2,4 MHz** gehen Sie bitte wie folgt vor:

Betätigen Sie beide Displaytasten gleichzeitig (Start/Stop und On/Off) [A14, A15], die Programmanzeige im Display [A12] blinkt nun (P1 od. P2).

Stellen Sie durch Drücken der Tasten Start/Stop [A15] (Einstellung nach unten) oder der Taste On/Off [A14] (Einstellung nach oben) das gewünschte Verneblerprogramm ein (P1 od. P2) 10 Sekunden nach dieser Einstellung erlischt das

Blinken auf dem Display [A12] und der **VENTA-NEB®-ir 2,4 MHz** zeigt das gewählte Programm an.

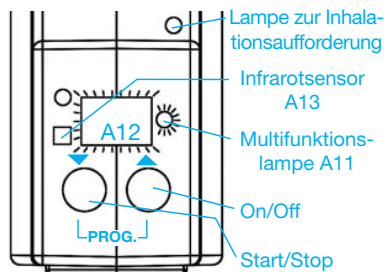
Die Bedienung des Gerätes erfolgt wie im Kapitel 7.0 beschrieben.

Einstellung:

Beide Sensortasten gleichzeitig drücken:
Anzeige blinkt

Linke Taste **Start/Stop** [A15] drücken:
Wert nach unten verstellen.

Rechte Taste **On/Off** [A14] drücken:
Wert nach oben verstellen.



Bei Nichtbetätigung der Tasten wird der eingestellte Wert nach ca. 10 Sekunden gespeichert.

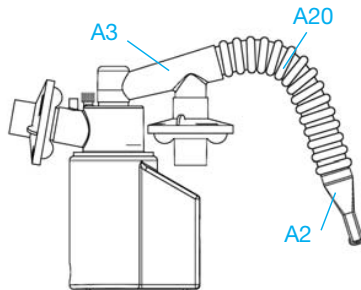
HINWEIS

Beim Betätigen der Sensortasten [A14,A15] wird die gewünschte Einstellung am Gerät durch einmaliges (kurzes) Antippen aktiviert. Ein längeres Halten bzw. Drücken der Tasten hat zur Folge, dass die jeweilige Einstellung aktiviert/deaktiviert/aktiviert/deaktiviert...(Ein/Aus/Ein/Aus...).usw. wird.

Wir möchten Sie daher anhalten, die zwei Sensortasten nur durch kurzes Antippen zu betätigen.

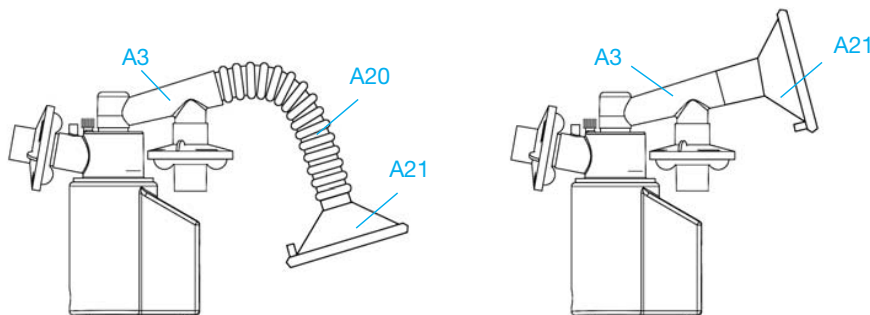
8.0 Einsatz eines Verlängerungs-schlauches bei liegender Inhalation

Ein Verlängerungsschlauch [A20] kann eingesetzt werden, wenn das Gerät vom Patienten in liegender Position benutzt wird. Dazu wird der Schlauch zwischen Mundstück [A2] und Ausatemteil [A3] positioniert.



8.1 Einsatz einer Maske für Inhalation (bei Kindern)

Zur Inhalation kann auch eine Gesichtsmaske, insbesondere bei Kindern, eingesetzt werden. Dies ist sowohl bei direkter Konnektion der Maske am Ausatemteil [A3], sowie mittels Einsatz eines Verlängerungsschlauches möglich. Dazu wird die Maske [A21] mit einem Adapter am Ausatemteil [A3], oder beim Einsatz eines Verlängerungsschlauches [A20] an diesem positioniert.



9.0 Reinigung

Durch sorgfältiges Beachten der unten aufgeführten Schritte, kann die Leistung maximiert und die Lebensdauer Ihres Ultraschallverneblers **VENTA-NEB®-ir** verlängert werden.

ACHTUNG

Um das Risiko einer etwaigen Infektion durch kontaminiertes Zubehör zu vermeiden, empfehlen wir die Angaben des Herstellers zu befolgen.

WARNUNG

Vor der Reinigung Ihres Ultraschallverneblers bitte den Netzstecker ziehen.

9.1 Reinigung der Kunststoffteile

Reinigung von Vernebleroberteil [A4] mit Dichtring und Prallplatte(n), Ausatemteil [A3], Filtergehäusen [A8/A9] und Mundstück [A2]).

Die oben beschriebenen Teile sind bei einmaliger täglicher Inhalation, nach der Inhalation, bei Medikamentenwechsel, oder bei mehrmaliger Inhalation nach der letzten Inhalation zu reinigen.

Die Teile sind bis 134°C temperaturstabil und müssen spätestens nach 24 Stunden wie folgt gereinigt werden:

Die Reinigung zu Hause sollte wie folgt durchgeführt werden:

- 9.11** Vernebleroberteil [A4] mit Dichtring und Prallplatte(n), Ausatemteil [A3], Filtergehäusen [A8/A9] und Mundstück [A2] voneinander trennen. Die Prallplatte kann durch die obere Öffnung nach unten herausgedrückt werden.
- 9.12** Das Zubehör mit warmem Leitungswasser oder in der Spülmaschine täglich reinigen.
- 9.13** Die Kunststoffteile nach der Reinigung für ca. 10 min in einem Topf auskochen.
- 9.14** Danach die Einzelteile an der Luft trocknen lassen (Abtrocknen mit einem Handtuch könnte eine Kontamination bzw. Verunreinigung verursachen).
- 9.15** Bei Verwendung eines Mikrowellendampfsterilisators bitte separate Bedienungsanleitung beachten. Die sich am Oberteil befindliche Luer/Lock-Verschlußkappe [A7], darf **N I C H T** in der Mikrowelle gereinigt bzw. sterilisiert werden.
- 9.16** Alle Teile wieder zusammenbauen. Falls die Prallplatte aus dem Vernebleroberteil [A4] entfernt wurde, bitte überprüfen, ob diese wieder richtig eingesetzt wurde.
- 9.17** Alle klarsichtigen Teile [A2, A3, A4, A7, A8] sind bis 134°C temperaturstabil.

ACHTUNG

Den Ultraschallvernebler **VENTA-NEB®-ir** [A1] niemals in ein Mikrowellengerät geben.

WICHTIGER HINWEIS

Vernebleroberteil [A4] mit Dichtring und Prallplatte(n), Ausatemteil [A3], Filtergehäusen [A8/A9] und Mundstück [A1], sowie Luer/Lock-Verschlußkappe [A7], sollten bei mehrmaliger täglicher Benutzung nach 3 Monaten gewechselt werden. Bei einmaliger täglicher Inhalation sind die Artikel nach Verschleiß und hygienischem Zustand zu wechseln.

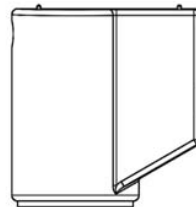
9.2 Kontaktflüssigkeitsbehälter und Gehäuse von VENTA-NEB®-ir**WARNUNG**

Das Gehäuse des Ultraschallverneblers niemals in Wasser oder in eine Reinigungslösung tauchen.

9.21 Vor der Reinigung den Netzstecker [A17] vom Gerät entfernen.

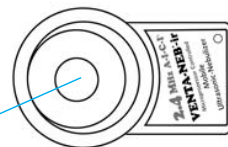
9.22 Das Gehäuse nur mit einem feuchten Tuch abwischen.

9.23 Die Kontaktflüssigkeit nach der letzten täglichen Inhalation ausschütten. Die Innenseite des Kontaktflüssigkeitsbehälters mit einem Tuch behutsam trockenwischen. Nach der Reinigung das Gerät auf den Kopf stellen (auf eine saugfähige Unterlage) und in dieser Position bis zur nächsten Benutzung trocknen lassen.



9.24 1-2 mal wöchentlich sollte der Ultraschallschwinger (am Boden des Wasserbehälters) mit einem Wattestäbchen vorsichtig (in kreisenden Bewegungen) gereinigt werden.

USV-Ansicht von oben



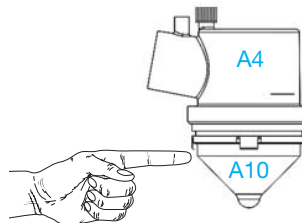
Schwinger mittels Wattestäbchen mit kreisenden Bewegungen reinigen

VORSICHT

Nicht mit scharfen Gegenständen am Ultraschallschwinger kratzen. Niemals zu fest auf den Ultraschallschwinger (am Boden des Wasserbehälters) drücken. Nichtbeachtung kann zu Beschädigungen führen.

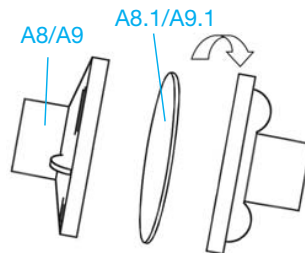
10.0 Wechsel Medikamentenbecher [A10]

Wenn Sie das Oberteil [A4] von dem Gerät entfernen, ist der Medikamentenbecher [A10] durch die 4 Nasen mit dem Oberteil verbunden. Der Medikamentenbecher wird durch seitlichen Druck vom Oberteil gelöst.



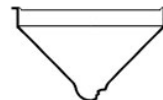
10.1 Wechselintervalle Filtermembrane und Medikamentenbecher

- 10.10** Der Wechsel des Medikamentenbechers muss aus Gründen der Dosiersicherheit täglich vorgenommen werden.
- 10.11** Die Ausatemfiltermembrane [A8.1] ist täglich zu wechseln.
- 10.12** Bei mehrmaligen täglichen Inhalationen kann ein zusätzlicher Wechsel der Filtermembrane [A8.1] notwendig sein (Ausatemwiderstandserhöhung der Filtermembrane).
- 10.13** Der Einatemfilter [A9.1] ist wöchentlich zu wechseln.
- 10.14** Das Filtergehäuse [A8/A9] entgegen dem Uhrzeigersinn drehen, um das Filtergehäuse [A8/A9] zu öffnen.
- 10.15** Filtermembrane [A8.1/A9.1] austauschen.
- 10.16** Filtergehäuse [A8/A9] durch Drehen im Uhrzeigersinn wieder verschließen.



HINWEIS

Die Medikamentenbecher sind Einwegbehälter und müssen aus hygienischen und technischen Gründen täglich gewechselt werden (siehe Kapitel 10.1). Das Nichteinhalten der vorgeschriebenen Wechselintervalle kann zu Deformationen des Medikamentenbechers [A10] führen. Diese Mikroverformungen des Medikamentenbechers [A10] können die Leistung des Ultraschallverneblers entscheidend verringern.



mikroverformter
Becher

11.0 Wartung




Eine Wartung mit anschließender STK-Prüfung muss alle zwei Jahre durchgeführt werden. Die Wartung darf nur von NEBU-TEC GmbH oder einem eigens dafür autorisierten und qualifizierten NEBU-TEC Fachhändler durchgeführt werden.

WARNUNG

Nicht das Gehäuse öffnen. Nichtbeachtung führt zu Garantieverlust.

12.0 Hinweise zur Fehlersuche

Wenn Sie glauben, dass Ihr Ultraschallvernebler nicht richtig funktioniert, nehmen Sie sich bitte die Zeit, die möglichen Mängel zu überprüfen bzw. zu beheben, bevor Sie das Gerät reklamieren.

Symptome	Mögliche Ursachen	Fehlerbehebung
Displayanzeige  (LB/Leere Batterie)	1. Netzteil defekt 2. Akku leer	1. Hersteller oder Händler verständigen 2. Akku laden
Displayanzeige  (LH/keine Kontaktflüssigkeit)	1. Keine Kontaktflüssigkeit im Behälter 2. Steriles oder zu reines Wasser eingefüllt.	1. 45 ml Kontaktflüssigkeit einfüllen (Sensor bedecken) 2. ca. 1 ml Leitungswasser zu den 45 ml Kontaktflüssigkeit zufügen.
Displayanzeige  (SA/Salzerkennung)	1. Salzhaltige oder verunreinigte Flüssigkeit eingefüllt (z.B. Leitungswasser, NaCl, Mineralwasser)	1. Vorsichtig mehrmals mit destilliertem Wasser auswaschen. Sensor im Kontaktflüssigkeitsbehälter vorsichtig mit Wattestäbchen oder ähnlichem reinigen, nochmals mit destilliertem Wasser auswaschen und anschließend den Kontaktflüssigkeitsbehälter neu befüllen.

Aerosolabgabe verringert (Restmenge zu hoch)	<ol style="list-style-type: none"> 1. Verbrauchter oder beschädigter Medikamentenbecher. 2. Kontaktflüssigkeitsstand im Kontaktflüssigkeitsbehälter zu hoch/niedrig. 3. Kontaktflüssigkeitsbehälter nicht ordnungsgemäß gereinigt. 4. Mehrere Medikamentenbecher eingesetzt. 	<ol style="list-style-type: none"> 1. Medikamentenbecher erneuern. 2. Kontaktflüssigkeitsbehälter mit 45 ml destilliertem Wasser befüllen (Messbecher mit Markierung nutzen). 3. Gerät der Anleitung entsprechend reinigen. 4. Nur einen Medikamentenbecher einsetzen.
Gerät erzeugt kein Aerosol	<ol style="list-style-type: none"> 1. Mehrere Medikamentenbecher eingesetzt. 2. Verbrauchter oder beschädigter Medikamentenbecher eingesetzt. 3. Gerät ist nicht an Stromquelle angeschlossen. 4. Keine Kontaktflüssigkeit im Kontaktflüssigkeitsbehälter eingefüllt. 5. Keine Flüssigkeit (Medikamentenlösung) im Medikamentenbecher. 	<ol style="list-style-type: none"> 1. Nur einen Medikamentenbecher einsetzen. 2. Neuen Medikamentenbecher einsetzen. 3. Gerät an Strom anschließen. 4. Kontaktflüssigkeitsbehälter bis zur richtigen Höhe befüllen. 5. Medikamentenbecher befüllen.
Ein- oder Ausatmung erschwert	<ol style="list-style-type: none"> 1. Filtermembrane ist verstopft bzw. durchnässt. 2. Vernebleroberteil ist nicht richtig befestigt. 	<ol style="list-style-type: none"> 1. Filtermembrane wechseln 2. Prüfen, ob das Vernebleroberteil richtig befestigt ist.

13.0 Technische Daten des Ultraschallverneblers VENTA-NEB®-ir

Größe	98 x 66 x 105 mm
Gewicht des Grundgerätes	280 g
Stromversorgungsarten	Netzgerät 110/230 VAC
.....	12 V Kfz-Adapter Zigarettenanzünder
.....	12 V Akku
Elektrische Versorgung	12 VDC, 1,5 A Maximum
Stromverbrauch bei Betrieb	18 Watt Maximum
Ultraschallfrequenz	2,4 MHz (nominal)
MMAD	2,3 µm (mit grüner Prallplatte)
Fassungsvermögen des Medikamentenbechers	7,5 ml Maximum
Fassungsvermögen des Kontaktflüssigkeitsbehälters	45 ml
Elektrische Schutzklasse	II Typ B

14.0 Zubehör / Bestellinformationen VENTA-NEB®-ir

Artikelnummer	Bezeichnung	VPE/Mengen
VN-100/2	VENTA-NEB®-ir 2,4 MHz	1
VN-MCA	Microprocessor Controlled Accu ON-2000	1
VN-100Z	12 V KFZ-Adapter Zigarettenanzünder	1
VN-100N	Netzteil FW 7555M/12 110/230 VDC	1
	(altern. lieferbar mit internat. Adaptern)	

Nicht autoklavierbare Teile:

VN-102	Medikamentenbecher unsteril	1
VN-106	Schlauchsystem 22m/15w	1
VN-109	Filtermembrane	10
VN-111	Sauerstoffschlauch Luer/Lock	1
VN-115	Safetybox mit Verschlußstopfenset	1
VN-116	Luer/Lock-Verschlußkappe	1
VN-118	Meßbecher	1
VN-122	Spezial-Maske > Kinder – Größe 1 mit expiratorischem Ventil	1
	Kinder/0-1 kg Körpergewicht	
VN-123	Spezial-Maske > Kinder – Größe 2 mit expiratorischem Ventil	1
	Kinder/1-8 kg Körpergewicht	
VN-124	Maske > Kinder – Größe 3 mit expiratorischem Ventil	1
	Kinder/8- kg Körpergewicht	

Autoklavierbare Teile - 134°C

VN-101	Filtergehäuse m. Ventil	1
VN-103	Oberteil	1
VN-103 komplett...	Oberteil mit Dichtring, 4 Prallplatten und	1
	Luer/Lock Verschußkappe	
VN-103 internat....	Oberteil mit Dichtring, blauer Prallplatte	1
	Luer/Lock Verschußkappe	
VN-104	Ausatenteil	1
VN-105	Mundstück	1
VN-110	Dichtring	1
VN-114	Mikrowellen-Dampf-Sterilisator	1
VN-117B	Prallplatte Blau – autoklavierbar - 3,2 µm	1
VN-117G	Prallplatte Grün - autoklavierbar - 2,3 µm	1
VN-117R	Prallplatte Rot - autoklavierbar - 3,8 µm	1
VN-117Y	Prallplatte Gelb - autoklavierbar - 4,5 µm	1
VN-117	Prallplatten-Set (Blau - Grün - Rot - Gelb)	1
VN-B-109	Verlängerungsschlauch gerade 22 AD / 15 ID	1
	Drehkonnektor 15 AD Innen glatt, 20 cm lang	
VB 3 Mon.	Autoklavierbare Teile für VENTA-NEB®-ir Heimtherapie	1
	für 3 Monate (inkl. 2 Filtergehäusen, Mundstück, Ausatem-	
	teil, Oberteil m. Prallpl., Dichtring u. Luer/Lock- Verschußkappe*	
VB 3 Monate	Kompl. VB's für VENTA-NEB®-ir Heimtherapie	1
	für 3 Monate (inkl. autoklavierbarer Teile, 100 Filter-	
	membranen und 100 Medikamentenbechern)	

* Die Luer/Lock-Verschußkappe ist nicht zum Autoklavieren oder Reinigen in der Mikrowelle geeignet

15.0 Garantie

Wir gewähren Ihnen auf den Ultraschallvernebler **VENTA-NEB®-ir** 24 Monate Garantie ab dem Verkaufsdatum.

16.0 Konformitätserklärung

Hersteller: **NEBU-TEC** med. Produkte Eike Kern GmbH
Kreuzfeldring 17
63820 Elsenfeld - GERMANY

Tel.: 06022-610 62 0
Fax: 06022-610 62 99
e-mail: nebu-tec@t-online.de
web: <http://www.nebu-tec.de>

Produktbezeichnung: **VENTA-NEB®-ir**
Typ, Modell: VN-100/4-2,4 MHz

Hiermit erklären wir, dass das oben genannte Produkt den Anforderungen der EG Richtlinie 93/42/EWG entspricht.

**Angewandte Normen:**

Qualitätssicherungssystem
Sicherheits-Norm
Sicherheits-Norm (POMS)
EMV Norm
Risikomanagement

DIN EN ISO 13485:2003
DIN EN 60601-1:1996
DIN EN 60601-1-4:1996
DIN EN 60601-1-2:2002
DIN EN 14971:2001

17.0 Garantiekarte zum Abtrennen/Warranty Card (tear-off card)

Garantiekarte/Warranty Card

Typ/Type: VN-100/4-2,4 MHz

Gerätenummer/Serial Number:

Kaufdatum/Purchase Date:

Benutzer, Händler/User, Dealer

Name:

Straße, Adresse/Street, Address:

.....

PLZ, Ort/Zip Code, Town:

.....

Land/Country:

Stempel/Stamp:

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1.0 IEC Symbols



Attention, consult operating instructions



Protection class II equipment



Type B application part



Class AP equipment



1275

2.0 Important Safeguards

Each handling of the device requires the exact understanding and observance of the present operating instructions.

In any case, the liability for the safe functioning of the device passes over to the user, if intervention by third persons or handling not according to the intended use occur.

Important information is highlighted by these terms:

DANGER

Urgent safety information for hazards that might cause serious injury.

WARNING

Important information for operating steps that might cause malfunctions of the device.

CAUTION

Information preventing damage to the product.

NOTE

Information to which you should pay particular attention.

[Components – see Sketch 4.0]

Please read the operating instructions carefully before the first operation of the product. Keep the operating instructions in a safe place.

DANGER

1. Always unplug the device immediately after use.
2. Do not use the device while taking a bath.
3. Do not place the device where it can fall into water.
4. Do not immerse the device in water or other liquids.
5. Do not use the device when it has fallen into water. Unplug it immediately.
6. Do not use the device under rain.
7. Do not use the device near flammable agents
8. Never insert hands or fingers into the contact fluid chamber or the medicine cup while the device is operating.

ENGLISH

WARNING

1. Activated HF-Communication equipment (like cellular phones, etc.) nearby the **VENTA-NEB®-ir** may affect its proper function.
2. Electric equipment should never be left unattended when plugged in.
3. Close supervision is necessary when the device is used by or near children or invalids.
4. Only use this device for the intended purposes as described in this operating instructions.
Do not use accessories not recommended by the manufacturer.
5. Never operate this product if
 - a) the power cord or the plug are damaged.
 - b) the device is not working properly.
 - c) the device has been dropped or damaged.
 - d) the device fell into water. In such cases return the device to the manufacturer or an authorised NEBU-TEC service dealer for inspection and repair.
6. Keep the power cord away from heated surfaces.
7. Place the device on a flat and solid surface in such way that no air openings are blocked.
8. Never use the device while you are sleeping.
9. Never insert any object into the openings of the equipment.
10. Never use the dish washer or microwave oven for cleaning the Ultrasonic Nebulizer (never expose the device to direct microwave radiation).

11. When cleaning the contact fluid chamber pay close attention to that no moisture can penetrate the housing from outside.
12. Change the contact fluid (distilled water) every 24 hours.
13. Do not use any cleaning solutions, vinegar, hot or even boiling water, etc... for cleaning the **control unit, the contact fluid chamber, the transducer or the sensor**.
14. Do not use cleaning solutions on aqueous alkaline basis, aromatic hydrocarbons, ammonia and amines for cleaning the **autoclaveable plastic parts**. Use cleaners on saturated aliphatic hydrocarbon basis, alcohols, dilute mineral acids, neutral and acid salt solution instead.

NOTE

While the **VENTA-NEB®-ir** is in operation no measures need to be taken regarding the electromagnetic compatibility.

Never lend the device to third persons.

Only inhale the medication prescribed by the physician.

Upon longer use the device may heat up on the bottom side.

3.0 Intended Purpose

Your **VENTA-NEB®-ir** Ultrasonic Nebulizer is a portable device designed to deliver aerosols of different particle sizes (see section 3.3). This ensures an optimum deposition of the medication.

3.1 Explanation on Operating Modes/Nebulization Programs

In order to allow the user to control which program is set and activated the active program briefly (for app. 1 second) appears in the display after the Ultrasonic Nebulizer was connected to the electric circuit.

- **VENTA-NEB®-ir** 2,4 MHz: 2 Programs (P1 or P2)

3.2 Function of A-I-C-I® for spontaneously breathing patients/home therapie

A-I-C-I® (active intermitted controlled inhalation)

When the device has been put into operation it indicates when and how often the patient should breathe in (inhale).

Acoustic signal:

Exhalation

Acoustic and optic signal (green light [A11.1]): Inhalation

Due to this inhalation-scheme, a more efficient and a precise dosage can be guaranteed.

The produced vapour can be inhaled through the mouthpiece (or mask). The exhalation also takes place over the mouthpiece [A2] or the face mask and is controlled by valves installed inside the filter shell [A8, A9] that cannot be interchanged. These filters prevent any leakage of aerosol into the air and thus form a closed system of the nebulization unit.

Located on top of the Dome [A4] of device is a Luer/Lock Connection [A6] where the medication can be added without opening the nebulization unit.

This connection can also be used to add oxygen.

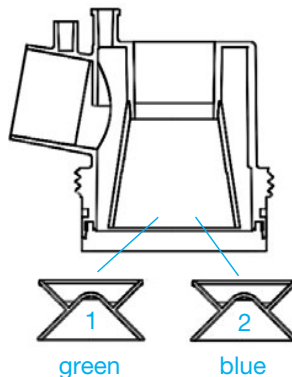
3.3 Aerosol Spectrum (Particle Sizes)

The particle size (MMAD(Mass Median Aerodynamic Diameter in μm) of the aerosol using

the green baffle plate and VENTAVIS[®] solution is 2.3 μm ,

the blue baffle plate and VENTAVIS[®] solution is 3.2 μm .

Baffle Plate 1 (VN-117G)	green colour	MMAD 2.3 μm measured with VENTAVIS [®]
Baffle Plate 2 (VN-117B)	blue colour	MMAD 3.2 μm measured with VENTAVIS [®]

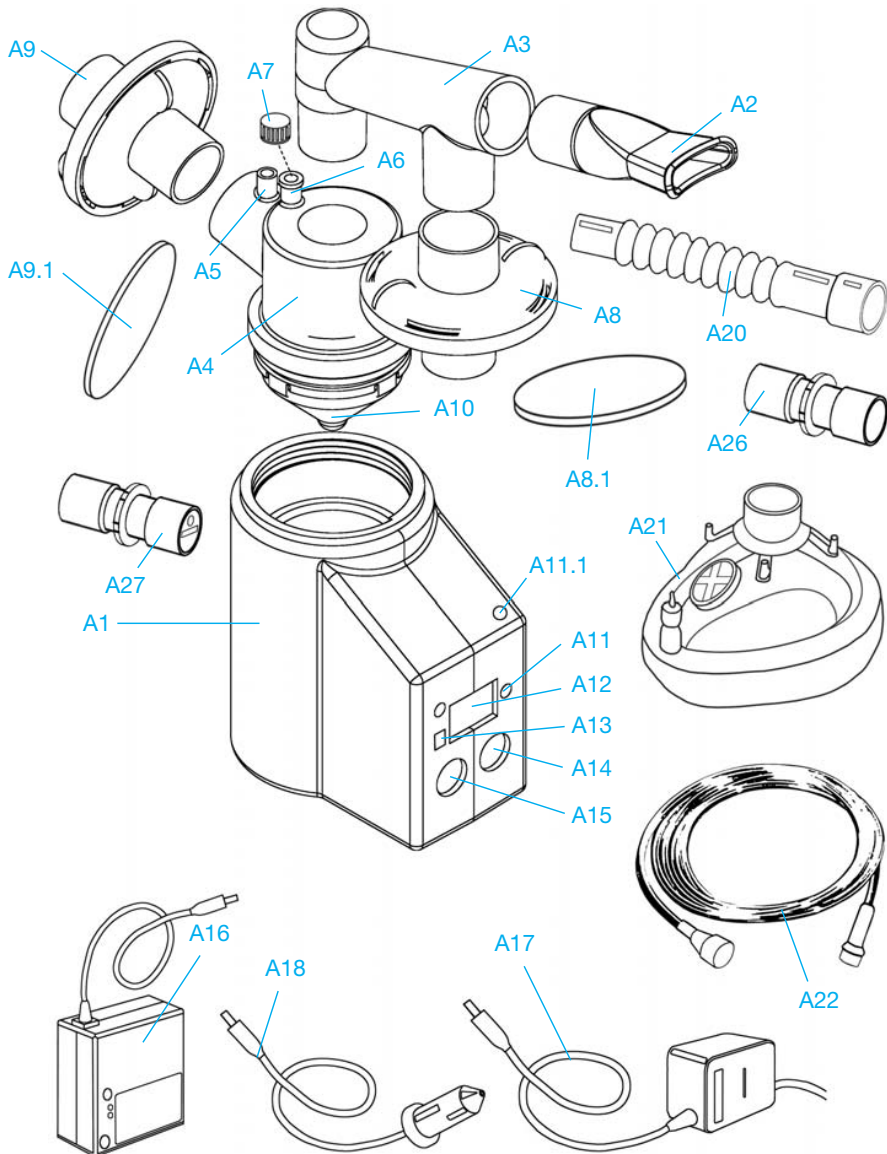


NOTE

The **VENTA-NEB[®]-ir** can be adjusted to patient-specific/individual inhalation patterns. However, only the manufacturer or the treating physician are authorized to perform such adjustments.

4.0 Important Parts of Your Ultrasonic Nebulizer VENTA-NEB®-ir

ENGLISH

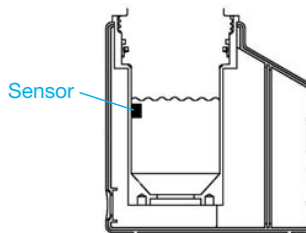


- A1** VENTA-NEB®-ir Ultrasonic Nebulizer
- A2** Mouthpiece (Art. VN-105)
- A3** Exhalation Piece (Art. VN-104)
- A4** Dome (Art. VN-103) with Sealing Ring (Art. VN-110), Baffle Plate (Art. VN-117B/G/R/Y) and Luer/Lock Protecting Cap (Art. VN-116)
- A5** Rest for Luer/Lock Protecting Cap
- A6** Luer/Lock Connection
- A7** Luer/Lock Protecting Cap (Art. VN-116)
- A8** Exhalation Filter Shell with Valve (Art. VN-101)
- A8.1** Exhalation Filter Membrane (Art. VN-109)
- A9** Inhalation Filter Shell with Valve (Art. VN-101)
- A9.1** Inhalation Filter Membrane (Art. VN-109)
- A10** Medicine Cup (VN-102)
- A11** Multifunctional Indicator Light
- A11.1** Light as a request to inhale
- A12** Display
- A13** Infrared Sensor
- A14** On/Off Button
- A15** Start/Stop Button
- A16** Rechargeable Battery Pack (Art. VN-MCA)
- A17** AC Power Adapter 110-230/230 VAC (Art. VN-100N)
- A18** 12 VDC Car Power Cord for Cigarette Lighter Socket (Art. VN-100Z)
- A20** Tube Extension 22 OD/15 ID (Art. VN-B-109)
- A21** Face Mask for Children with Expiration Valve, Sizes 1/2/3 (Art. VN-122/123/124)
- A22** Luer/Lock Tube for Oxygen or Medicine Nebulization Control Line (Art. VN-111)
- A26** Adapter for adaptation of face mask 22 OD/22 OD - 15 ID (Art. VN-119)
- A27** Inhalation trainer

5.0 How to Operate Your VENTA-NEB®-ir Ultrasonic Nebulizer (USN) upon Inhalation through the Mouthpiece

Preparing the Ultrasonic Nebulizer

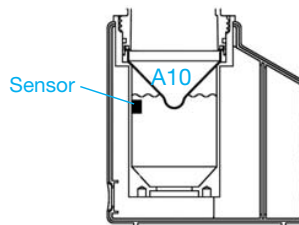
- 5.01** Remove the power plug [A17] so that the nebulizer will not start running unintentionally.
- 5.02** Fill the contact fluid chamber up to the blue mark with distilled or demineralised water using the measuring cup. The sensor must be entirely covered with this contact fluid (app. 45 ml).



WARNING

The utilization of other contact fluids (e.g. tap water, sterile water or saline) is strictly prohibited as this may result in an essential affection of the device's performance and even the total failure of the device.

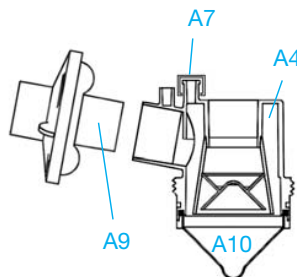
- 5.03** Insert the medicine cup [A10]. Please ensure that the tip of the medicine cup is submersed in the contact fluid.

**NOTE**

The medicine cup [A10] is a disposable article. Inspect it for any defect before each use.

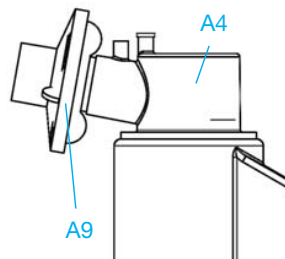
If the medicine cup is damaged or the unit is experiencing low output, replace the medicine cup or clean the transducer.

- 5.04** Make sure that the baffle plate is properly fastened inside the dome [A4], a sealing ring is inserted, and the Luer/Lock protecting cap [A7] is connected to the dome.



- 5.05** Insert the filter shell with the inhalation filter membrane [A9] in the designated opening of the dome [A4].

- 5.06** Place the dome [A4] with the inhalation filter [A9] oriented towards the back of the unit, and turn it clockwise until you hear a clear click. This sound is generated when the medicine cup [A10] connects to the dome [A4].

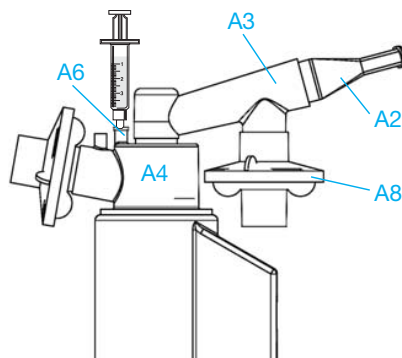


5.07 Assemble the mouthpiece [A2], the exhalation piece [A3], the exhalation filter shell [A8] and connect them to the dome [A4].

5.08 Fill-in the fluid (medicine solution) to inhale through the designated opening [A6] (Luer/Lock connection) in the top of the dome [A4] by means of a syringe.

5.09 Close the Luer/Lock connection [A6] with the protecting cap [A7].

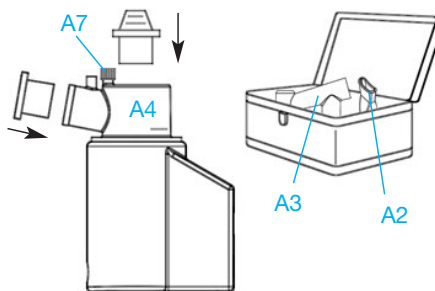
5.10 Put the device into operation as described in section 7.0 – 7.1 of this operating instructions.



ENGLISH

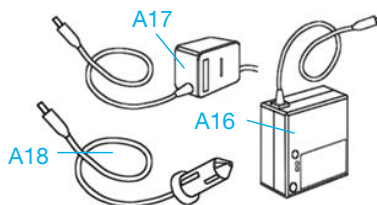
NOTE

Upon several inhalations per day or when the device is transported between the single inhalations, the dome [A4] should be closed with the delivered Luer/Lock protecting cap [A7] and the two plugs for hygienic reasons. Then the mouthpiece [A2], the exhalation piece [A3] and the two filter shells [A8, A9] have to be stowed in the safety box.



6.0 Power Supply of the Ultrasonic Nebulizer VENTA-NEB®-ir

You can connect the Ultrasonic Nebulizer to three different power sources: alternating current - 110/220 volts, direct current - 12 volts (car), or rechargeable battery pack.



6.1 AC Operation

Plug the AC Power Adapter [A17] in an AC power outlet and the other end in the unit (110 or 220/230 volts).

NOTE for AC Operation

Do not use the device while taking a bath.

Do not place the device where it can fall into water.

Do not immerse the device in water or other liquids.

Do not use the device when it has fallen into water.

Immediately unplug the power adapter.

6.2 DC Operation

Plug the car power cord [A18] in the cigarette lighter socket and the other end in the unit.

NOTE for DC operation

Do not use the device while taking a bath.

Do not place the device where it can fall into water.

Do not immerse the device in water or other liquids.

Do not use the device when it has fallen into water.

Immediately unplug the car power cord.

6.3 Instruction guide of the rechargeable battery pack

Please find enclosed the separate instructin guide.

6.3.1 For charging purposes please only use the original power cord [A17]. Therefore, please connect the plug of the power cord to the rechargeable battery pack.

6.3.2 Depending on the charging-state, the rechargeable battery pack takes up to 12 hours until it is completely charged.

6.3.3 Please do not use the rechargeable battery pack while it is being charged.

6.3.4 Shortly after the charging process has been fnished, the letter combination „E“, „n“, „d“ (= Ende) appears successively on the display. Now the rechargeable battery pack is ready for use.

6.3.5 If you do not want to use the rechargeable battery pack immediately after charging it, it can remain connected to the power cord for a period of time (even a few days) although the charging process has been finished.

6.3.6 Please only connect the rechargeable battery pack to the **VENTA-NEB®-ir** while executing the inhalation.

6.3.7 Please remove the plug of the rechargeable battery pack from the nebulizer after each inhalation.

6.3.8 In order to check the charging-state, please push the button (Akkutest) for approximately 3 seconds. Shortly after having pushed this button, the charging capacity is shown on the display in per cent (%).



ENGLISH

Please ignore the green, red or orange LED display on the battery pack itself, since these indicator lights do not have any significance concerning the actual state of charge of the battery pack.

When the rechargeable battery pack is completely charged, it is sufficient for approximately one week.

NOTE for battery operation

Do not use the device while taking a bath.
Do not place the device where it can fall into water.
Do not immerse the device in water or other liquids.
Do not use the device when it has fallen into water.
Immediately unplug the rechargeable battery pack.

CAUTION

To prevent damage to the Ultrasonic Nebulizer and to ensure compliance with the EMV EN 55011 guidelines, only the original AC power adapter [A17] or the original rechargeable battery pack [A16] may be used.

NOTE

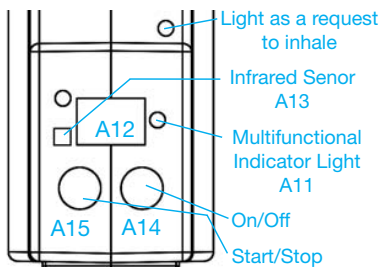
Bring defective battery packs to battery disposal points for proper disposal, or send them back to NEBU-TEC GmbH.

7.0 Using Your Ultrasonic Nebulizer VENTA-NEB®-ir

After connecting the **VENTA-NEB®-ir** to the power circuit the inhalation program set by your physician briefly appears in the display [A12] (for app. 1 sec.).

7.01 In order to turn on the ultrasonic nebulizer, please push the button „On/Off“ – a yellow light appears on the nebulizer. The amount of inspiration cycles is now shown on the display.

7.02 In order to commence the inhalation, please push the button “start/stop” [A15] (accompanied by an acoustic signal) and



breathe out slowly. Please breathe in regularly and slowly when noticing the next acoustic signal which is accompanied by an optic signal at the same time [A11.1] (green light appears). After breathing in, please shortly stop breathing and then breathe out slowly. (In order to learn how to inhale correctly and to optimize the inhalation, please use the “inhalation coach” [A27]). Please connect the „inhalation coach“ to the inhalation filter shell.

7.03 To interrupt the aerosol production, please press the **Start/Stop** sensor button [A15]. The multifunctional indicator light [A11] is yellow and the display [A12] shows PA (Pause). To continue the aerosol production press the **Start/Stop** sensor button [A15] again.

The display will change from "PA" to the time mode, the multifunctional indicator light is green, the nebulization is continued.

The inhalation is terminated when En (End) appears in the display. At the same time an acoustic signal sounds at the end of the inhalation.

7.04 Place the mouthpiece [A2] in your mouth and inhale the medicated aerosol over the inhalation filter and the valve by taking a slow, deep breath. The exhalation also takes place over the mouthpiece and the exhalation filter with valve.

The inhalation instruction: ‘The Right Way to Inhale’ is available separately.

7.05 Continue to inhale until the respective nebulization program has expired. This is indicated by an acoustic signal and En (End) in the display. The inhalation period can depend on the respective nebulization program as well as the breathing technique of the patient.

7.06 Switch off the device after the inhalation is finished (**On/Off**) [A14] and disconnect the Ultrasonic Nebulizer from the respective power source.

NOTE

The device is equipped with a multifunctional indicator light which indicates the operating state.

ADVICE

The device has a multi-function light [A11] and a light as a request to inhale [A11.1].

Light as a request to inhale [A11.1]:

Green light is on - inhalation starts.

Green light is off - end of the inhalation or pause.

Multifunctional indicator light [A11]:

Yellow light - Device ready for operation

Green light - Device in operation

Red light - Malfunction

Display readings [A12]



(LB) Low Battery...



(LH) Low Hydrogen - contact fluid missing, or wrong contact fluid in the chamber



(SA) Impure or saline fluid in the unit (tap water, sodium chloride, mineral water, etc.)



(PA) Pause



(En) End...

NOTE

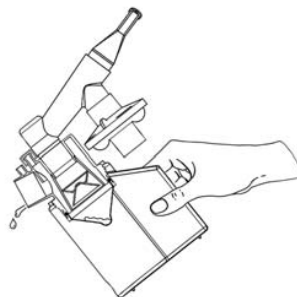
As the proportion of active substance of your medicine within the remaining residue is too small, please do not use it again for a new inhalation.

In order to check the amount of residue you may turn the device upside down and read the residue at the graduation on the dome [A4].

The device is leak-proof up to 7,5 ml of liquid in the medicine cup.

NOTE

The residue of the medication remaining in the medicine cup has to be emptied after each inhalation. In order to empty the residue remove the inhalation filter [A9] and pour out the remaining medication by tilting the device.



7.1 Programming and Settings of the Ultrasonic Nebulizer

The selection of the nebulization programs has to be conducted by the attending physician and authorized technical personnel that works on the order of the physician's recommendation.

The manufacturer of the **VENTA-NEB®-ir** does not issue any recommendations regarding the dosage of medication. For the inhalative application please carefully read the enclosed leaflet of the medicine.

7.1.1 Programming and Settings of the VENTA-NEB®-ir 2.4 MHz

The **VENTA-NEB®-ir 2.4 MHz** Ultrasonic Nebulizer allows the patient to choose between 2 different nebulization programs.

After connecting the **VENTA-NEB®-ir 2.4 MHz** to the electric circuit the set nebulization program is briefly (app. 1 second) shown in the display.

P1 Program 1 5,0 µg active substance on the mouthpiece 25 inhal. cycles

P2 Program 2 2,5 µg active substance on the mouthpiece 10 inhal. cycles

Changing the Nebulization Program on the VENTA-NEB®-ir 2.4 MHz

To change the programs on the **VENTA-NEB®-ir 2.4 MHz** please proceed as follows: Press both display buttons (Start/Stop and On/Off) [A14, A15] at the same time, the program shown in the display [A12] flashes (**P1** or **P2**).

Set the desired program (**P1** or **P2**) by pressing the button Start/Stop [A15] (down) or the button On/Off [A14] (up). 10 seconds after this procedure the display [A12] stops flashing and the **VENTA-NEB®-ir 2.4 MHz** shows the selected program.

For the operation of the device refer to the description in Chapter 7.0.

Setting:

Pressing both sensor buttons at the same time:

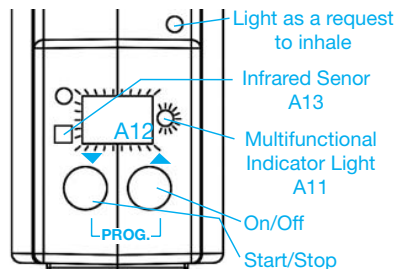
Display blinks

Pressing left button **Start/Stop [A15]**:

Set lower value.

Pressing right button **On/Off [A14]**:

Set higher value.



If no button is pressed the set value will be stored after app. 10 seconds.

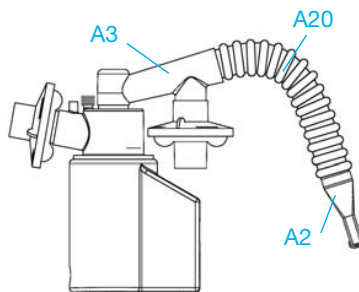
NOTE

The desired setting of the device is activated by one (short) tap on the sensor buttons [A14, A15]. If the buttons are pressed or held for a longer time this results in the respective setting being activated/deactivated/activated/deactivated...(on/off/on/off...) and so on.

Therefore we would like to ask you to actuate the two sensor buttons by shortly tapping on them.

8.0 Using an Tube Extension for Inhalation when Lying

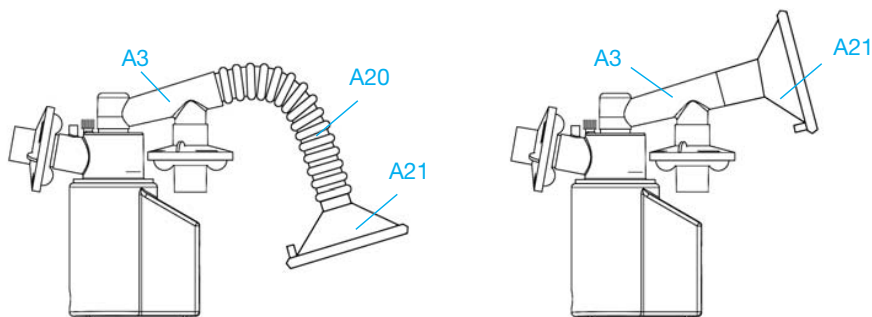
An extension hose or tube extension [A20] can be used if the patient is lying while using the device. Then the hose [A20] is inserted between the mouthpiece [A2] and the exhalation piece [A3].



8.1 Using a Face Mask for the Inhalation (for Children)

A facial mask [A21] can be used especially for children. The face mask can either be directly connected to the exhalation piece [A3] or to a tube extension [A20], if necessary.

Then the face mask is connected to the exhalation piece [A3] or to the extension hose [A20] by means of an adapter.



9.0 Cleaning

Carefully following the steps outlined below will help maximise the performance and extend the service life of your Ultrasonic Nebulizer **VENTA-NEB®-ir**.

WARNING

To prevent possible risk of infection from contaminated accessory parts, we recommend to follow the manufacturer's instructions.

DANGER

Please disconnect the device from any power source before cleaning your Ultrasonic Nebulizer.

9.1 Autoclaveable Plastic Parts

Cleaning the Dome [A4] and Baffle Plate(s), Exhalation Piece [A3], Filter Shells [A8/A9] and Mouthpiece [A2].

The parts described above have to be cleaned upon inhalation once a day after the inhalation, or upon change of medication or inhalation several times a day after the last inhalation.

The parts are temperature resistant up to 134°C and have to be cleaned after 24 hours at the latest as follows:

How you should clean your device at home:

9.11 Disassemble the Dome [A4] with Sealing Ring and Baffle Plate(s), Exhalation Piece [A3], both Filter Shells [A8/A9] and Mouthpiece [A2]. You can push out the baffle plate through the opening in the top of the dome.

- 9.12 Clean the accessories under warm tap water or in the dishwasher every day.
- 9.13 After cleaning, scald out the plastic parts in a pot for app. 10 min.
- 9.14 Then allow the component parts to air dry. (Towel drying could lead to contamination or soiling.)
- 9.15 If using the microwave vapour sterilizer, please follow the separate operating manual. The Luer/Lock protecting cap [A7] must **N O T** be cleaned or sterilized in the microwave oven.
- 9.16 Carefully reassemble all parts. If the baffle plate has been removed from the dome [A4], please check that it was properly reinstalled.
- 9.17 All transparent parts [A2, A3, A4, A7, A8] are autoclaveable up to 134°C.

WARNING

Never put the Ultrasonic Nebulizer **VENTA-NEB®-ir** [A1] in a microwave oven.

IMPORTANT NOTE

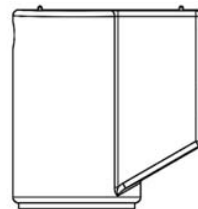
The Dome [A4] with Sealing Ring and Baffle Plate(s), Exhalation Piece [A3], both Filter Shells [A8/A9] and Mouthpiece [A2] as well as Luer/Lock protecting cap [A7] should be replaced after 3 months when the unit is used several times a day. If used only once a day the parts mentioned above have to be replaced depending on wear and hygienic condition.

9.2 Contact Fluid Chamber and Control Unit of the VENTA-NEB®-ir

DANGER

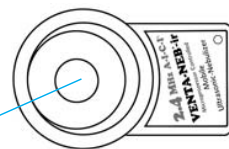
Never submerge the control unit of the Ultrasonic Nebulizer in water or cleaning solution.

- 9.21 Before cleaning the control unit, disconnect the AC power adapter [A17] from the device.
- 9.22 Only wipe the exterior of the control unit with a damp cloth.
- 9.23 Empty the contact fluid chamber after the last daily inhalation. Then carefully dry the inside of the contact fluid chamber with a soft cloth. After the cleaning turn the device upside down (place it on an absorbent pad) and let it dry in this position until the next utilization.



- 9.24** The transducer (at the bottom of the contact fluid chamber) should be cleaned once a week by wiping carefully with a cotton swab (performing rotating movements).

Top view of the USN



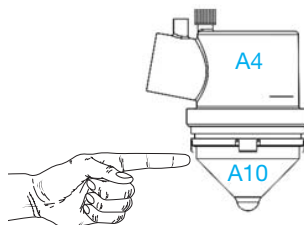
Clean transducer with a cotton swab performing rotating movements

CAUTION

Do not scratch the transducer with sharp-edged items.
Never push too hard on the transducer (at the bottom of the contact fluid chamber). Doing so may lead to damages.

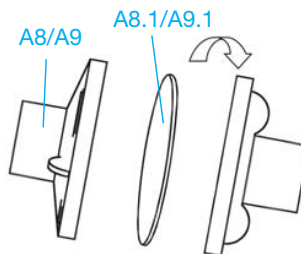
10.0 Changing the Medicine Cup [A10]

If you remove the dome [A4] from the device, the medicine cup [A10] is attached to the dome by four lugs. The medicine cup is removed from the dome by pressing on them laterally.



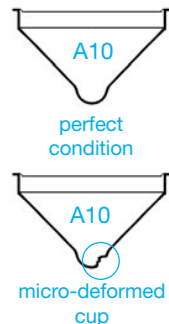
10.1 Replacement Intervals for Filter Membrane and Medicine Cup

- 10.10** In order to ensure a secure dosing the medicine cup has to be replaced every day.
- 10.11** The exhalation filter membrane [A8.1] has to be changed every day.
- 10.12** Upon inhalation several times a day it might be necessary to change the filter membrane [A8.1] more often (increase of the exhalation resistance of the filter membrane).
- 10.13** The inhalation filter [A9.1] has to be changed once a week.
- 10.14** Turn the filter shell [A8/A9] anticlockwise to open it.
- 10.15** Replace the filter membrane [A8/A9].
- 10.16** Turn the filter shell [A8/A9] clockwise to close it again.



NOTE

The medicine cups are disposables and have to be replaced every day for hygienic and technical reasons (see section 10.1). Failure to observe the provided replacement intervals may lead to deformations of the medicine cup [A10]). These micro deformations of the medicine cup [A10] may considerably reduce the output of the Ultrasonic Nebulizer



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11.0 Maintenance



The **VENTA-NEB®-ir** Ultrasonic Nebulizer should be serviced every 2 years. All maintenance must be performed by NEBU-TEC GmbH or an authorised and qualified NEBU-TEC service dealer.

DANGER

Do not remove the exterior cabinet of the control unit. Non-compliance will lead to loss of warranty.

12.0 Notes on Troubleshooting

If you think your device is not working properly, please take a few moments to check for and repair these possible causes before you complain about it.

Symptoms	Possible Causes	Remedies
Display  (LB/Low Battery)	1. AC adapter defective. 2. Battery empty.	1. Contact manufacturer or dealer 2. Charge battery pack.
Display  (LH/Low Hydrogen)	1. No contact fluid in the contact fluid chamber. 2. Sterile or too pure water in the contact fluid chamber	1. Fill in 45 ml of contact fluid (sensor must be covered). 2. Add app. 1 ml of tap water to the 45 ml of contact fluid.

Display



(SA/Salt Recognition)

1. Saline or impure fluid in the contact fluid chamber (e.g. tap water, NaCl, mineral water).	1. Carefully wash out the chamber several times with distilled water. Carefully clean the sensor in the contact fluid chamber with a cotton swab or something alike, rinse out the chamber again with distilled water, and then refill the contact fluid chamber.
1. Worn or damaged medicine cup. 2. Contact fluid level in the contact fluid chamber too high/low. 3. Contact fluid chamber was not cleaned properly. 4. Multiple medicine cups placed in the contact fluid chamber.	1. Replace medicine cup. 2. Fill contact fluid chamber with distilled water up to the mark (app. 45 ml). 3. Clean device according to instructions. 4. Only place one medicine cup.
1. Multiple medicine cups placed in the contact fluid chamber. 2. Worn or damaged medicine cup placed in the chamber. 3. Device not connected to power source. 4. No contact fluid filled in the contact fluid chamber. 5. No fluid (medicine solution) in the medicine cup.	1. Insert only one medicine cup. 2. Insert new medicine cup. 3. Connect device to power source. 4. Fill contact fluid chamber to proper level. 5. Fill medicine cup.
1. Filter membrane is clogged or soaked. 2. Dome is not properly fastened.	1. Replace filter membrane. 2. Check if dome is properly fastened.

Reduced aerosol output
(too much residue)Device does not
produce aerosolInhalation or exhalation
is more difficult

13.0 Specifications VENTA-NEB®-ir

Size	98 x 66 x 105 mm
Weight, control unit	280 g
Types of power supply	110/230 VAC power adapter
.....	12 VDC car power cord (cigarette lighter)
.....	12 VDC battery pack
Power supply	12 VDC, 1.5 A maximum
Operating power consumption	18 Watt maximum
Ultrasonic frequency	2.4 MHz (nominal)
MMAD	2.3 µm (green coloured baffle plate)
Medicine cup capacity	7.5 ml maximum
Contact fluid chamber capacity	45 ml
Electric protection class	II Type B

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14.0 Accessories / Order Information VENTA-NEB®-ir

Article Number	Designation	Packing Unit/Quantity
VN-100/2	VENTA-NEB®-ir 2.4 MHz	1
VN-MCA	Microprocessor controlled rechargeable battery pack ON-2000	1
VN-100Z	12 VDC Car Power Cord (Cigarette Lighter)	1
VN-100N	AC Power Adapter FW 7555M/12 110/230 VAC (available with international Adapters upon request)	1
Non-autoclaveable parts		
VN-102	Medicine Cup, non sterile	1
VN-106	Hose System 22 male/15 female	1
VN-109	Filter Membrane	10
VN-111	Luer/Lock Oxygen Hose	1
VN-115	Safety Box with Set of Protecting Plugs	1
VN-116	Luer/Lock Protecting Cap	1
VN-118	Measuring Cup	1
VN-122	Special Face Mask >Children – Size 1 with Expiratory Valve Children/0-1 kg Body Weight	1
VN-123	Special Face Mask >Children – Size 2 with Expiratory Valve Children/1-8 kg Body Weight	1
VN-124	Face Mask >Children – Size 3 with Expiratory Valve Children/8- kg Body Weight	1

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Autoclaveable parts - 134°C

VN-101	Filter Shell w/ Valve	1
VN-103	Dome	1
VN-103 komplett	Dome with Sealing Ring, 4 Baffle Plates and Luer/Lock Protecting Cap	1
VN-103 internat.	Dome with Sealing Ring, Blue Baffle Plate and Luer/Lock Protecting Cap	1
VN-104	Exhalation Piece	1
VN-105	Mouthpiece	1
VN-110	Sealing Ring	1
VN-114	Microwave Vapour Sterilizer	1
VN-117B	Baffle Plate Blue - autoclaveable - 3.2 µm	1
VN-117G	Baffle Plate Green - autoclaveable - 2.3 µm	1
VN-117R	Baffle Plate Red - autoclaveable - 3.8 µm	1
VN-117Y	Baffle Plate Yellow - autoclaveable - 4.5 µm	1
VN-117	Set of Baffle Plates (Blue - Green - Red - Yellow)	1
VN-B-109	Tube Extension 22 OD/15 ID, 20 cm long	1
VB 3 Mon.	Autoclaveable Parts for VENTA-NEB®-ir Home Therapy – for 3 Months (incl. 2 Filter Shells, Mouthpiece, Exhalation Piece, Dome with Baffle Pl., Sealing Ring and Luer/Lock Protecting Cap*	1
VB 3 Mon.	Compl. Consumables for VENTA-NEB®-ir Home Therapy – for 3 Months (incl. Autoclaveable Parts, 100 Filter Membranes and 100 Medicine Cups)	1

* The Luer/Lock protecting cap is not suitable for autoclaving or cleaning in the microwave oven

15.0 Warranty

2 years starting from purchase date

16.0 Declaration of Conformity

Manufacturer: **NEBU-TEC** med. Produkte Eike Kern GmbH

Address: Kreuzfeldring 17
63820 Elsenfeld - GERMANY

Tel.: (+49) (0)6022-610 62-0

Fax: (+49) (0)6022-64 98 12

e-mail: nebu-tec@t-online.de

web: <http://www.nebu-tec.de>

Product Designation: **VENTA-NEB®-ir**

Model/Type: VN-100/2-2.4 MHz

We herewith declare that the above product complies with the requirements of EC Directive 93/42/EEC.



Applied standards:

Quality System	DIN EN ISO 13485:2003
Electrical Safety	DIN EN 60601-1:1996
Electrical Safety (POMS)	DIN EN 60601-1-4:1996
EMV Standards	DIN EN 60601-1-2:2002
Risk Management	DIN EN 14971:2001

17.0 Warranty Card

See page 27.

